

**I. KASSIRSKY AND N. PLOTNIKOV**

*DISEASES  
OF WARM  
LANDS*

---





*I. KASSIRSKY, N. PLOTNIKOV*

---

DISEASES  
OF  
WARM LANDS

(A CLINICAL MANUAL)

TRANSLATED FROM THE RUSSIAN

BY  
MIRIAM KATZ

PEACE PUBLISHERS

MOSCOW

TO THE READER

Peace Publishers would be glad to have your opinion regarding this book, its translation, design and printing, and to receive any suggestions from you.

Please write to 2, Pervy Rizhsky Pereulok, Moscow, U.S.S.R.

## CONTENTS

Foreword .....	15
Introduction .....	17
Malaria. <i>I. Kassirsky</i> .....	21
History .....	21
Etiologic Agents of Malaria .....	23
<i>Anopheles</i> Mosquitoes, Their Propagation and Role in the Transmission of Malaria .....	33
Geographical Distribution of Malaria .....	37
Forms of Malaria .....	39
Clinical Aspects .....	42
Certain Aspects of the Pathogenesis of Malaria .....	49
Plasmodia Carriers .....	52
Classification of Malaria .....	53
Fresh (Recent) Malaria Infection .....	54
Pernicious Forms of Malaria .....	59
Lesions of Systems and Organs in Malaria .....	71
Metamalarial Diseases .....	77
Malaria and Pregnancy .....	79
Malaria in Children .....	81
Duration of Malaria .....	82
Immunity .....	84
Prognosis .....	85
Laboratory Diagnosis in Malaria and Its Importance .....	86
Basic Principles of Therapy .....	87
Antimalaria Preparations .....	91
Treatment Schemes .....	100
Out-patient Treatment for Malaria Patients .....	104
Treatment of Pernicious Forms of Malaria .....	104
Symptomatic Therapy in Pernicious (Comatose) Malaria ...	105
Treatment of Malarial Hemoglobinuria (Blackwater Fever) .	105
Specific Management of Malaria Therapy in Children .....	106
Individual Chemoprophylaxis .....	107

·Leishmaniasis .....	108
Visceral Leishmaniasis .....	110
Cutaneous Leishmaniasis .....	130
American Cutaneous Leishmaniasis .....	142
Sudanese (Egyptian) Cutaneous Leishmaniasis .....	144
Trypanosomiasis. <i>N. Plotnikov</i> .....	145
African Trypanosomiasis .....	145
American Trypanosomiasis .....	152
Tick-borne Relapsing Fevers. <i>I. Kassirsky</i> .....	159
Historical Data .....	159
The Causative Agent .....	160
Epidemiology .....	160
Different Types of Tick-borne Relapsing Fever and Their Geographical Distribution .....	163
Laboratory Diagnosis .....	167
Clinical Aspects .....	168
Differential Diagnosis .....	171
Treatment .....	171
Prophylaxis .....	172
Leptospiral Diseases of Man .....	174
Historical Data .....	174
Spirochetel Jaundice (Icterohemorrhagic Leptospirosis, Weil-Vasilyev Disease). .....	176
Marsh Fever .....	184
Leptospiral Diseases of the Far East .....	186
Rostov Infectious Jaundice .....	187
Seven-day Fever (Nanukayami) .....	188
Autumnal Fever A .....	188
Autumnal Fever B .....	188
Hasamiyami Leptospirosis .....	188
Leptospiral Diseases of the Tropics .....	189
Yaws (Frambesia). <i>N. Plotnikov</i> .....	191
Historical Data .....	191
Etiology .....	191
Epidemiology .....	191
Geographical Distribution .....	193
Clinical Aspects .....	193
Diagnosis .....	198
Pathology .....	199
Treatment .....	199
Prophylaxis .....	199
Pinta .....	200
Etiology .....	200
Epidemiology .....	200

Geographical Distribution .....	200
Clinical Aspects .....	200
<b>Bejel .....</b>	<b>202</b>
Prophylaxis .....	202
Treatment .....	202
<b>Amebiasis. I. Kassirsky .....</b>	<b>203</b>
Historical Data .....	203
Parasitology .....	205
Epidemiology and Geographical Distribution .....	208
The Problem of Amebiasis .....	209
Amebiasis Classification .....	212
Clinical Aspects .....	213
Differential Diagnosis .....	214
Pathogenesis and Pathology .....	215
Treatment .....	216
Prophylaxis .....	219
<b>Chronic Ulcerative Colitis (Non-protozoan) .....</b>	<b>220</b>
Etiology .....	220
Clinical Aspects .....	221
Treatment .....	223
Prophylaxis .....	225
<b>Schistosome Diseases (Schistosomiasis). N. Plotnikov .....</b>	<b>226</b>
Genitourinary Schistosomiasis .....	227
Intestinal Schistosomiasis .....	231
Treatment of Genitourinary and Intestinal Schistosomiasis ..	235
Schistosomiasis Japonica .....	238
Prophylaxis .....	242
Schistosome Dermatitis .....	242
<b>Clonorchiasis .....</b>	<b>246</b>
Historical Data .....	246
Etiology .....	246
Epidemiology .....	247
Geographical Distribution .....	248
Clinical Aspects .....	248
Diagnosis .....	249
Pathology and Pathogenesis .....	250
Treatment .....	251
Prophylaxis .....	252
<b>Opisthorchiasis Viverrini .....</b>	<b>253</b>
Etiology .....	253
Epidemiology .....	254
Geographical Distribution .....	254
Clinical Aspects .....	254

Prophylaxis .....	254
Treatment .....	254
Amphymerosis (Opisthorchiasis Noverca) .....	255
Metagonimosis .....	256
Historical Data .....	256
Etiology .....	256
Epidemiology .....	257
Geographical Distribution .....	258
Clinical Aspects .....	258
Diagnosis .....	258
Prognosis .....	258
Pathology and Pathogenesis .....	258
Treatment .....	259
Prophylaxis .....	259
Heterophyiasis .....	260
Etiology .....	260
Epidemiology .....	261
Geographical Distribution .....	261
Clinical Aspects .....	261
Diagnosis .....	261
Prognosis .....	262
Pathology and Pathogenesis .....	262
Prophylaxis .....	262
Treatment .....	262
Nanophyetosis .....	263
Paragonimiasis .....	264
Historical Data .....	264
Etiology .....	264
Epidemiology .....	265
Geographical Distribution .....	265
Clinical Aspects .....	266
Diagnosis .....	267
Pathology and Pathogenesis .....	267
Treatment .....	268
Prophylaxis .....	268
Fascioliasis .....	269
Historical Data .....	269
Etiology .....	269
Epidemiology .....	270
Geographical Distribution .....	271
Clinical Aspects .....	271
Diagnosis .....	273
Prognosis .....	273

Pathology and Pathogenesis .....	273
Treatment .....	274
Prophylaxis .....	275
Fasciolopsiasis .....	276
Historical Data .....	276
Etiology .....	276
Epidemiology .....	276
Geographical Distribution .....	277
Clinical Aspects .....	277
Pathology and Pathogenesis .....	278
Treatment .....	279
Prophylaxis .....	279
Echinostomiasis .....	280
Euparyphiasis .....	281
Echinochasmiasis .....	282
Himasthlosiasis .....	283
Gastrodisciasis .....	284
Plagiorchiasis .....	285
Watsoniasis .....	286
Eurythremasiasis .....	287
Sparganosis .....	288
Etiology .....	288
Epidemiology .....	289
Geographical Distribution .....	289
Clinical Aspects .....	289
Diagnosis .....	289
Prognosis .....	289
Treatment .....	290
Prophylaxis .....	290
Bertielliasis .....	291
Raillietiniasis .....	292
Ancylostomidoses (Hookworm Diseases) .....	293
Etiology .....	293
Epidemiology .....	294
Geographical Distribution .....	295
Clinical Aspects .....	295
Diagnosis .....	299
Prognosis .....	299
Pathology and Pathogenesis .....	299
Treatment .....	299
Prophylaxis .....	302

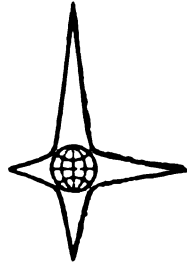
<b>Filarial Diseases (Filariasis)</b> .....	<b>303</b>
<b>Wuchereriasis</b> .....	<b>303</b>
<b>Onchocerciasis</b> .....	<b>310</b>
<b>Loaiasis</b> .....	<b>314</b>
<b>Acanthocheilonemiasis</b> .....	<b>316</b>
<b>Dirofilarioses</b> .....	<b>317</b>
<b>Mansonelliasis</b> .....	<b>318</b>
<b>Strongyloidiasis</b> .....	<b>319</b>
<b>Etiology</b> .....	<b>319</b>
<b>Epidemiology</b> .....	<b>320</b>
<b>Geographical Distribution</b> .....	<b>320</b>
<b>Clinical Aspects</b> .....	<b>320</b>
<b>Diagnosis</b> .....	<b>321</b>
<b>Prognosis</b> .....	<b>322</b>
<b>Pathology and Pathogenesis</b> .....	<b>322</b>
<b>Treatment</b> .....	<b>323</b>
<b>Prophylaxis</b> .....	<b>323</b>
<b>Dracunculosis. I. Kassirsky</b> .....	<b>324</b>
<b>Historical Data</b> .....	<b>324</b>
<b>Etiology</b> .....	<b>325</b>
<b>Geographical Distribution and Epidemiology</b> .....	<b>326</b>
<b>Clinical Aspects</b> .....	<b>328</b>
<b>Treatment</b> .....	<b>328</b>
<b>Lagochilascaridosis. N. Plotnikov</b> .....	<b>331</b>
<b>Hepaticolosis</b> .....	<b>332</b>
<b>Trichostrongyliasis</b> .....	<b>334</b>
<b>Strongyloidosis</b> .....	<b>336</b>
<b>Syngamosis</b> .....	<b>338</b>
<b>Gongylonemiasis</b> .....	<b>339</b>
<b>Gnathostomiasis</b> .....	<b>340</b>
<b>Abreviatosis</b> .....	<b>341</b>
<b>Thelaziasis</b> .....	<b>342</b>
<b>Diectophymosis</b> .....	<b>343</b>
<b>Rickettsioses (Rickettsial Diseases)</b> .....	<b>344</b>
<b>Endemic or Murine Typhus</b> .....	<b>344</b>
<b>Rocky Mountain Spotted Fever</b> .....	<b>347</b>
<b>Boutonneuse (Marseilles) Fever</b> .....	<b>351</b>
<b>South and East African Tick-bite Fevers</b> .....	<b>354</b>
<b>North Queensland Tick Typhus</b> .....	<b>356</b>
<b>Tsutsugamushi Disease (Japanese Fever)</b> .....	<b>355</b>
<b>Q Fever or Pneumorickettsiosis</b> .....	<b>360</b>
<b>Pappataci Fever. I. Kassirsky</b> .....	<b>365</b>
<b>Historical Data</b> .....	<b>365</b>
<b>Etiology and Epidemiology</b> .....	<b>366</b>



Geographical Distribution .....	367
Clinical Aspects .....	368
Diagnosis .....	370
Treatment .....	370
Prophylaxis .....	371
<b>Dengue .....</b>	<b>373</b>
Historical Data .....	373
Etiology and Epidemiology .....	374
Geographical Distribution .....	375
Clinical Aspects .....	375
Diagnosis .....	377
Differential Diagnosis .....	377
Prognosis .....	378
Pathology .....	378
Treatment .....	378
Prophylaxis .....	378
<b>Yellow Fever .....</b>	<b>379</b>
Historical Data .....	379
Etiology .....	380
Epidemiology .....	381
Geographical Distribution .....	383
Clinical Aspects .....	384
Diagnosis .....	386
Prognosis .....	387
Pathology .....	387
Pathogenesis .....	387
Treatment .....	388
Prophylaxis .....	388
<b>Psittacosis. <i>N. Plotnikov</i> .....</b>	<b>390</b>
Historical Data .....	390
Etiology .....	390
Epidemiology .....	390
Geographical Distribution .....	391
Clinical Aspects .....	391
Diagnosis .....	392
Prognosis .....	392
Pathology .....	392
Treatment .....	392
Prophylaxis .....	392
<b>Lymphogranuloma Venereum .....</b>	<b>393</b>
Etiology .....	393
Epidemiology .....	393
Geographical Distribution .....	393
Clinical Aspects .....	393
Diagnosis .....	394

Pathology .....	395
Treatment .....	395
Prophylaxis .....	395
<b>Granuloma Inguinale .....</b>	<b>396</b>
Etiology .....	396
Epidemiology and Geographical Distribution .....	396
Clinical Aspects .....	397
Diagnosis .....	398
Prognosis .....	398
Treatment .....	398
Prophylaxis .....	399
<b>Bartonellosis .....</b>	<b>400</b>
Historical Data .....	400
Etiology .....	400
Epidemiology and Geographical Distribution .....	401
Clinical Aspects .....	401
Diagnosis .....	402
Prognosis .....	402
Pathology and Pathogenesis .....	402
Treatment .....	402
Prophylaxis .....	403
<b>Mycoses (Mycotic Diseases) .....</b>	<b>404</b>
Maduromycosis .....	404
South American Blastomycosis .....	406
Coccidioidomycosis .....	408
Histoplasmosis .....	409
<b>Poisonous Fauna of Warm Lands .....</b>	<b>411</b>
Bite of the Karakurt (Black Widow Spider). <i>I. Kassirsky</i> ..	411
Scorpions .....	415
Poisonous Beetles .....	416
Snake Bite Poisoning. <i>N. Plotnikov</i> .....	417
<b>Sprue. <i>I. Kassirsky</i> .....</b>	<b>420</b>
Historical Data .....	420
Geographical Distribution .....	421
Clinical Aspects .....	421
Etiology and Pathogenesis .....	424
Prognosis .....	425
Treatment .....	425
<b>Protracted Enteritis of Warm Lands .....</b>	<b>426</b>
Treatment of Sprue and Chronic Fermentative Enteritis ....	428
<b>Beriberi .....</b>	<b>430</b>
Historical Data .....	430
Geographical Distribution .....	430

<b>Etiology</b> .....	<b>431</b>
<b>Clinical Aspects</b> .....	<b>431</b>
<b>Pathogenesis</b> .....	<b>434</b>
<b>Prognosis</b> .....	<b>435</b>
<b>Treatment</b> .....	<b>435</b>
<b>Alimentary Toxicosis</b> .....	<b>437</b>
<b>Heliotrope Hepatitis (Heliotrope Disease)</b> .....	<b>437</b>
<b>Effect of Warm Climate on the Human Body</b> .....	<b>442</b>
<b>Heat Hyperpyrexia</b> .....	<b>444</b>
<b>Effect of Heat on Fluid-electrolyte Metabolism</b> .....	<b>447</b>
<b>Effect of Heat on the Digestive Function</b> .....	<b>452</b>
<b>Effect of Heat on the Cardiovascular System</b> .....	<b>455</b>
<b>Effect of Heat on the Skin</b> .....	<b>456</b>
<b>Personal Hygiene and Daily Routine</b> .....	<b>457</b>
<b>Index</b> .....	<b>459</b>



**PEACE**  
**PUBLISHERS**

**И. А. КАСИРСКИЙ, Н. Н. ПЛОТНИКОВ**

**БОЛЕЗНИ  
ЖАРКИХ СТРАН**

**ГОСУДАРСТВЕННОЕ ИЗДАТЕЛЬСТВО  
МЕДИЦИНСКОЙ ЛИТЕРАТУРЫ  
МЕДГИЗ МОСКВА**

*I. KASSIRSKY, N. PLOTNIKOV*

---

DISEASES  
OF  
WARM LANDS

(A CLINICAL MANUAL)

TRANSLATED FROM THE RUSSIAN

BY  
MIRIAM KATZ

PEACE PUBLISHERS

MOSCOW

**TO THE READER**

Peace Publishers would be glad to have your opinion regarding this book, its translation, design and printing, and to receive any suggestions from you.

Please write to 2, Pervy Rizhsky Pereulok, Moscow, U.S.S.R.

## CONTENTS

Foreword .....	15
Introduction .....	17
Malaria. <i>I. Kassirsky</i> .....	21
History .....	21
Etiologic Agents of Malaria .....	23
<i>Anopheles</i> Mosquitoes, Their Propagation and Role in the Transmission of Malaria .....	33
Geographical Distribution of Malaria .....	37
Forms of Malaria .....	39
Clinical Aspects .....	42
Certain Aspects of the Pathogenesis of Malaria .....	49
Plasmodia Carriers .....	52
Classification of Malaria .....	53
Fresh (Recent) Malaria Infection .....	54
Pernicious Forms of Malaria .....	59
Lesions of Systems and Organs in Malaria .....	71
Metamalarial Diseases .....	77
Malaria and Pregnancy .....	79
Malaria in Children .....	81
Duration of Malaria .....	82
Immunity .....	84
Prognosis .....	85
Laboratory Diagnosis in Malaria and Its Importance .....	86
Basic Principles of Therapy .....	87
Antimalaria Preparations .....	91
Treatment Schemes .....	100
Out-patient Treatment for Malaria Patients .....	104
Treatment of Pernicious Forms of Malaria .....	104
Symptomatic Therapy in Pernicious (Comatose) Malaria ...	105
Treatment of Malarial Hemoglobinuria (Blackwater Fever) .	105
Specific Management of Malaria Therapy in Children .....	106
Individual Chemoprophylaxis .....	107



Leishmaniasis .....	108
Visceral Leishmaniasis .....	110
Cutaneous Leishmaniasis .....	130
American Cutaneous Leishmaniasis .....	142
Sudanese (Egyptian) Cutaneous Leishmaniasis .....	144
Trypanosomiasis. <i>N. Plotnikov</i> .....	145
African Trypanosomiasis .....	145
American Trypanosomiasis .....	152
Tick-borne Relapsing Fevers. <i>I. Kassirsky</i> .....	159
Historical Data .....	159
The Causative Agent .....	160
Epidemiology .....	160
Different Types of Tick-borne Relapsing Fever and Their Geographical Distribution .....	163
Laboratory Diagnosis .....	167
Clinical Aspects .....	168
Differential Diagnosis .....	171
Treatment .....	171
Prophylaxis .....	172
Leptospiral Diseases of Man .....	174
Historical Data .....	174
Spirochetel Jaundice (Icterohemorrhagic Leptospirosis, Weil-Vasilyev Disease). .....	176
Marsh Fever .....	184
Leptospiral Diseases of the Far East .....	186
Rostov Infectious Jaundice .....	187
Seven-day Fever (Nanukayami) .....	188
Autumnal Fever A .....	188
Autumnal Fever B .....	188
Hasamiyami Leptospirosis .....	188
Leptospiral Diseases of the Tropics .....	189
Yaws (Frambesia). <i>N. Plotnikov</i> .....	191
Historical Data .....	191
Etiology .....	191
Epidemiology .....	191
Geographical Distribution .....	193
Clinical Aspects .....	193
Diagnosis .....	198
Pathology .....	199
Treatment .....	199
Prophylaxis .....	199
Pinta .....	200
Etiology .....	200
Epidemiology .....	200

Geographical Distribution .....	200
Clinical Aspects .....	200
<b>Bejel .....</b>	<b>202</b>
Prophylaxis .....	202
Treatment .....	202
<b>Amebiasis. I. Kassirsky .....</b>	<b>203</b>
Historical Data .....	203
Parasitology .....	205
Epidemiology and Geographical Distribution .....	208
The Problem of Amebiasis .....	209
Amebiasis Classification .....	212
Clinical Aspects .....	213
Differential Diagnosis .....	214
Pathogenesis and Pathology .....	215
Treatment .....	216
Prophylaxis .....	219
<b>Chronic Ulcerative Colitis (Non-protozoan) .....</b>	<b>220</b>
Etiology .....	220
Clinical Aspects .....	221
Treatment .....	223
Prophylaxis .....	225
<b>Schistosome Diseases (Schistosomiasis). N. Plotnikov .....</b>	<b>226</b>
Genitourinary Schistosomiasis .....	227
Intestinal Schistosomiasis .....	231
Treatment of Genitourinary and Intestinal Schistosomiasis ..	235
Schistosomiasis Japonica .....	238
Prophylaxis .....	242
Schistosome Dermatitis .....	242
<b>Clonorchiasis .....</b>	<b>246</b>
Historical Data .....	246
Etiology .....	246
Epidemiology .....	247
Geographical Distribution .....	248
Clinical Aspects .....	248
Diagnosis .....	249
Pathology and Pathogenesis .....	250
Treatment .....	251
Prophylaxis .....	252
<b>Opisthorchiasis Viverrini .....</b>	<b>253</b>
Etiology .....	253
Epidemiology .....	254
Geographical Distribution .....	254
Clinical Aspects .....	254

Prophylaxis .....	254
Treatment .....	254
Amphymerosis (Opisthorchiasis Noverca) .....	255
Metagonimosis .....	256
Historical Data .....	256
Etiology .....	256
Epidemiology .....	257
Geographical Distribution .....	258
Clinical Aspects .....	258
Diagnosis .....	258
Prognosis .....	258
Pathology and Pathogenesis .....	258
Treatment .....	259
Prophylaxis .....	259
Heterophyiasis .....	260
Etiology .....	260
Epidemiology .....	261
Geographical Distribution .....	261
Clinical Aspects .....	261
Diagnosis .....	261
Prognosis .....	262
Pathology and Pathogenesis .....	262
Prophylaxis .....	262
Treatment .....	262
Nanophyetosis .....	263
Paragonimiasis .....	264
Historical Data .....	264
Etiology .....	264
Epidemiology .....	265
Geographical Distribution .....	265
Clinical Aspects .....	266
Diagnosis .....	267
Pathology and Pathogenesis .....	267
Treatment .....	268
Prophylaxis .....	268
Fascioliasis .....	269
Historical Data .....	269
Etiology .....	269
Epidemiology .....	270
Geographical Distribution .....	271
Clinical Aspects .....	271
Diagnosis .....	273
Prognosis .....	273

Pathology and Pathogenesis .....	273
Treatment .....	274
Prophylaxis .....	275
Fasciolopsiasis .....	276
Historical Data .....	276
Etiology .....	276
Epidemiology .....	276
Geographical Distribution .....	277
Clinical Aspects .....	277
Pathology and Pathogenesis .....	278
Treatment .....	279
Prophylaxis .....	279
Echinostomiasis .....	280
Euparyphiasis .....	281
Echinochasmiasis .....	282
Himasthlosiasis .....	283
Gastrodisciasis .....	284
Plagiorchiasis .....	285
Watsoniasis .....	286
Eurythremasiasis .....	287
Sparganosis .....	288
Etiology .....	288
Epidemiology .....	289
Geographical Distribution .....	289
Clinical Aspects .....	289
Diagnosis .....	289
Prognosis .....	289
Treatment .....	290
Prophylaxis .....	290
Bertielliasis .....	291
Raillietiniasis .....	292
Ancylostomidoses (Hookworm Diseases) .....	293
Etiology .....	293
Epidemiology .....	294
Geographical Distribution .....	295
Clinical Aspects .....	295
Diagnosis .....	299
Prognosis .....	299
Pathology and Pathogenesis .....	299
Treatment .....	299
Prophylaxis .....	302

<b>Filarial Diseases (Filariasis)</b> .....	<b>303</b>
<b>Wuchereriosis</b> .....	<b>303</b>
<b>Onchocerciasis</b> .....	<b>310</b>
<b>Loiasis</b> .....	<b>314</b>
<b>Acanthocheilonemiasis</b> .....	<b>316</b>
<b>Dirofilarioses</b> .....	<b>317</b>
<b>Mansonelliasis</b> .....	<b>318</b>
<b>Strongyloidiasis</b> .....	<b>319</b>
<b>Etiology</b> .....	<b>319</b>
<b>Epidemiology</b> .....	<b>320</b>
<b>Geographical Distribution</b> .....	<b>320</b>
<b>Clinical Aspects</b> .....	<b>320</b>
<b>Diagnosis</b> .....	<b>321</b>
<b>Prognosis</b> .....	<b>322</b>
<b>Pathology and Pathogenesis</b> .....	<b>322</b>
<b>Treatment</b> .....	<b>323</b>
<b>Prophylaxis</b> .....	<b>323</b>
<b>Dracunculosis. I. Kassirsky</b> .....	<b>324</b>
<b>Historical Data</b> .....	<b>324</b>
<b>Etiology</b> .....	<b>325</b>
<b>Geographical Distribution and Epidemiology</b> .....	<b>326</b>
<b>Clinical Aspects</b> .....	<b>328</b>
<b>Treatment</b> .....	<b>328</b>
<b>Lagochilascaridosis. N. Plotnikov</b> .....	<b>331</b>
<b>Hepaticolosis</b> .....	<b>332</b>
<b>Trichostrongyliasis</b> .....	<b>334</b>
<b>Strongyloidosis</b> .....	<b>336</b>
<b>Syngamosis</b> .....	<b>338</b>
<b>Gongylonemiasis</b> .....	<b>339</b>
<b>Gnathostomiasis</b> .....	<b>340</b>
<b>Abreviatosis</b> .....	<b>341</b>
<b>Thelaziasis</b> .....	<b>342</b>
<b>Diocetophymosis</b> .....	<b>343</b>
<b>Rickettsioses (Rickettsial Diseases)</b> .....	<b>344</b>
<b>Endemic or Murine Typhus</b> .....	<b>344</b>
<b>Rocky Mountain Spotted Fever</b> .....	<b>347</b>
<b>Boutonneuse (Marseilles) Fever</b> .....	<b>351</b>
<b>South and East African Tick-bite Fevers</b> .....	<b>354</b>
<b>North Queensland Tick Typhus</b> .....	<b>356</b>
<b>Tsutsugamushi Disease (Japanese Fever)</b> .....	<b>355</b>
<b>Q Fever or Pneumorickettsiosis</b> .....	<b>360</b>
<b>Pappataci Fever. I. Kassirsky</b> .....	<b>365</b>
<b>Historical Data</b> .....	<b>365</b>
<b>Etiology and Epidemiology</b> .....	<b>366</b>

Geographical Distribution .....	367
Clinical Aspects .....	368
Diagnosis .....	370
Treatment .....	370
Prophylaxis .....	371
<b>Dengue .....</b>	<b>373</b>
Historical Data .....	373
Etiology and Epidemiology .....	374
Geographical Distribution .....	375
Clinical Aspects .....	375
Diagnosis .....	377
Differential Diagnosis .....	377
Prognosis .....	378
Pathology .....	378
Treatment .....	378
Prophylaxis .....	378
<b>Yellow Fever .....</b>	<b>379</b>
Historical Data .....	379
Etiology .....	380
Epidemiology .....	381
Geographical Distribution .....	383
Clinical Aspects .....	384
Diagnosis .....	386
Prognosis .....	387
Pathology .....	387
Pathogenesis .....	387
Treatment .....	388
Prophylaxis .....	388
<b>Psittacosis. <i>N. Plotnikov</i> .....</b>	<b>390</b>
Historical Data .....	390
Etiology .....	390
Epidemiology .....	390
Geographical Distribution .....	391
Clinical Aspects .....	391
Diagnosis .....	392
Prognosis .....	392
Pathology .....	392
Treatment .....	392
Prophylaxis .....	392
<b>Lymphogranuloma Venereum .....</b>	<b>393</b>
Etiology .....	393
Epidemiology .....	393
Geographical Distribution .....	393
Clinical Aspects .....	393
Diagnosis .....	394

Pathology .....	395
Treatment .....	395
Prophylaxis .....	395
Granuloma Inguinale .....	396
Etiology .....	396
Epidemiology and Geographical Distribution .....	396
Clinical Aspects .....	397
Diagnosis .....	398
Prognosis .....	398
Treatment .....	398
Prophylaxis .....	399
Bartonellosis .....	400
Historical Data .....	400
Etiology .....	400
Epidemiology and Geographical Distribution .....	401
Clinical Aspects .....	401
Diagnosis .....	402
Prognosis .....	402
Pathology and Pathogenesis .....	402
Treatment .....	402
Prophylaxis .....	403
Mycoses (Mycotic Diseases) .....	404
Maduromycosis .....	404
South American Blastomycosis .....	406
Coccidioidomycosis .....	408
Histoplasmosis .....	409
Poisonous Fauna of Warm Lands .....	411
Bite of the Karakurt (Black Widow Spider). <i>I. Kassirsky</i> ..	411
Scorpions .....	415
Poisonous Beetles .....	416
Snake Bite Poisoning. <i>N. Plotnikov</i> .....	417
Sprue. <i>I. Kassirsky</i> .....	420
Historical Data .....	420
Geographical Distribution .....	421
Clinical Aspects .....	421
Etiology and Pathogenesis .....	424
Prognosis .....	425
Treatment .....	425
Protracted Enteritis of Warm Lands .....	426
Treatment of Sprue and Chronic Fermentative Enteritis ....	428
Beriberi .....	430
Historical Data .....	430
Geographical Distribution .....	430

<b>Etiology .....</b>	<b>431</b>
<b>Clinical Aspects .....</b>	<b>431</b>
<b>Pathogenesis .....</b>	<b>434</b>
<b>Prognosis .....</b>	<b>435</b>
<b>Treatment .....</b>	<b>435</b>
<b>Alimentary Toxicosis .....</b>	<b>437</b>
<b>Heliotrope Hepatitis (Heliotrope Disease) .....</b>	<b>437</b>
<b>Effect of Warm Climate on the Human Body .....</b>	<b>442</b>
<b>Heat Hyperpyrexia .....</b>	<b>444</b>
<b>Effect of Heat on Fluid-electrolyte Metabolism .....</b>	<b>447</b>
<b>Effect of Heat on the Digestive Function .....</b>	<b>452</b>
<b>Effect of Heat on the Cardiovascular System .....</b>	<b>455</b>
<b>Effect of Heat on the Skin .....</b>	<b>456</b>
<b>Personal Hygiene and Daily Routine .....</b>	<b>457</b>
<b>Index.....</b>	<b>459</b>





## **FOREWORD**

Specialists in all fields of medicine practising in the tropics, subtropics, or any other climatic zone should be familiar with the pathognomonics of diseases common to warm climates. The constantly expanding scope of travel between various countries and migration of the population are the cause of sporadic appearances in temperate and northern zones of so-called tropical diseases, brought in from without. Local doctors must therefore be conversant with the diagnosis and treatment of such diseases.

Long-term activities in the field of tropical medicine (both parasitogenic and otherwise) have led the authors to compile this manual containing descriptions of all the most important and widespread diseases of the tropics and subtropics.

Diseases less important and of controversial nosology are not presented.

This work is basically a clinical manual dwelling chiefly on the clinical findings, pathogenesis, and treatment of the ailments of hot climates. The epidemiologic, parasitologic, and prophylactic aspects are discussed briefly, only in so far as they are required for a full exposition of the problems involved in each nosologic form.

Moreover, the authors have found it desirable to discuss the clinical aspect and pathogenesis of climatic pathology proper in the torrid zones (effect of environmental heat on fluid and electrolyte metabolism, nutrition, the cardiovascular system, etc.).

The manual is intended for a wide range of medical specialists.



## INTRODUCTION

Diseases of warm lands are a peculiar field of pathology that has long been set apart as a separate discipline. The propagation of tropical diseases, diseases of hot climatic zones, is connected, first of all, with the torrid climate. This climate is characterised by a low changeability in the length of the day and intensive solar radiation varying but slightly throughout the year, owing to which a high atmospheric temperature is maintained; there are also considerable diurnal alterations in other climatic elements — humidity, precipitation, cloudiness, winds. The tropical climate is typical of a definite belt on both sides of the equator, limited by 23.5° N. and S. latitude. However, a purely geographical conception of the so-called tropical diseases would be wrong.

Certain endemic diseases characteristic of the tropics are also encountered in continental climates — from 23.5° to 38° N. lat., in the zones of torrid, arid steppelands.

We know that many infections can spread in any climate, any geographic zone, at any height above sea level. Such infections or infestations are called *cosmopolitan*. Among them are typhoid fever, typhus, louse-bite relapsing fever, measles, whooping cough, smallpox, etc.

Other infections are transmissible from man to man or from animal to man only in definite localities. They are called natural endemic diseases, or *diseases with natural endemic foci*. These diseases are subdivided into three groups, depending on the specific natural features and local climate required for their propagation.

The *first group* includes infections (infestations) the spread of which is connected with climate and soil, i. e., with inanimate nature. The *second group* includes diseases of man requiring vectors for the transmission of the infection. The *third group* comprises infections (infestations) peculiar to animals in certain natural foci, which can be transmitted to man through the agency of vectors.

*First group.* There are incommunicable diseases the pathogens of which must undergo certain transformations in definite environmental conditions (temperature, humidity, aeration) to become infestive. An illustrative example is ascariasis. The ascarid ova emerge from the intestine of an

infested human being in an immature state. To become infestive the ova must mature in the outer surroundings under certain conditions of temperature and moisture, must not be exposed to intensive insolation, and must have a sufficient supply of oxygen. An example of infestations of this group, encountered predominantly in warm lands, is ancylostomiasis (hookworm infestation). This type of infestation is peculiar to warm climates, as the maturation of the ova and development of the larvae take place in moist, warm soil. However, conditions of this type may be created artificially—in mines, for instance. Thus, miners are often subject to hookworm infestation in even comparatively cold climates.

The *second group* is quite voluminous. It includes diseases that require specific vectors for their propagation; such diseases are malaria, leishmaniasis, pappataci fever. These are the so-called transmissible infections, and they can only be spread in the localities inhabited by the specific xenogenic vectors of the causative agents, which must go through a definite developmental cycle in the vector to become infestive.

This large group of diseases (as well as the first group) is in its turn subdivided into: 1) cosmopolitan infections (infestations) such as malaria, a disease encountered in almost all latitudes; 2) infections endemic to the tropics, such as yellow fever, and 3) infections of the arid subtropics, the steppeland continental zone, such as pappataci fever, leishmaniasis, etc.

As regards this group of diseases it must be pointed out that some of the cosmopolitan parasitic infections it includes (for instance, malaria in the tropics and subtropics) are characterised by numerous epidemiological and clinical features, by reason of which they are included in manuals on tropical diseases (hence malaria is so comprehensively represented in the present manual).

Extremely important in the pathology of warm climates is the *third group of endemic infections* (infestations) that are *diseases with natural foci*. The majority of these diseases are transmissible to man, and their vectors are insects and ticks.

In the Soviet Union Y. Pavlovsky has studied and expanded the teachings on natural endemic foci of transmissible diseases. Y. Pavlovsky has given a comprehensive definition of natural endemic foci: "Natural endemicity of transmissible diseases is a phenomenon concomitant with the existence of generations upon generations of the etiologic agent, of its specific vector, and of the animal reservoirs of this agent for indefinitely protracted periods of time in their native environment, independent of man both in their past evolution and in its present phase".

The group of transmissible diseases with natural foci includes tick-borne relapsing fevers, cutaneous leishmaniasis, Russian Far East encephalitis, plague, tularemia, and others.

Tick-borne relapsing fever (spirochetosis) exists among a number of animal species—dogs and certain rodents—and its vectors are Ornithodoros ticks. Cutaneous leishmaniasis of the desert type is widespread among gerbils that populate the deserts and semideserts of Central Asia, Iran, Iraq, North and Central Africa; the vectors responsible for the transmis-

sion of the pathogen of this infection are *Phlebotomus* sandflies. Many analogous examples of transmissible endemic diseases with natural foci might be cited. The teachings on these diseases conform to the basic laws of Charles Darwin's theory of evolution: the development of transmissible diseases is due to the natural selection and struggle for existence of all living organisms — from viruses to parasites and vertebrates. Even such an infinitesimal organism as the Russian Far East encephalitis virus has ensured itself a stable existence, parasitising many inhabitants of the taiga and being transmitted from one animal to another by the agency of ticks; with the advent of man into the taiga the virus adapted itself to the human body as well. Moreover, this virus lives in the ticks for prolonged periods and is transmitted by a transovarian route to their progeny. A number of worm diseases also possesses natural foci; among them are trichinosis, dyphyllobothriasis, opisthorchiasis, Japanese schistosomiasis and others.

The *geographical propagation* of each natural endemic infection (infestation) is possible only within the area populated by specific vectors (first and second intermediaries) and the corresponding reservoir of the infection. This dissemination is connected with natural conditions (climate and microclimate) that favour the multiplication of the pathogen in the xenorganism (the vector) and the reproduction of the vector itself.

The above explains the existence and development in the tropics and relatively warm climates (and solely in these conditions) of absolutely definite infections (infestations) transmitted to man by definite vectors, whose existence is possible only in tropical or relatively hot zones. Such diseases are numerous. They are not, nor can they be, encountered in relatively cold or cold climatic zones, in so far as the determinant factors in their propagation are the vectors and the microbes that develop in the latter. Why are many transmissible and natural endemic diseases localised specifically in warm lands? The explanation evidently should be sought in the easier climatic conditions conducive to existence and reproduction (it is common knowledge that cold necessitates the development of more complex adaptative biological and physiological mechanisms). Naturally, even within their own habitat transmissible tropical diseases can develop only in the presence of definite and specific conditions — microclimate, epidemic, etc. These conditions depend on the number of pathogen-infested animals, on the density of this animal population, their migrations, fertility and mortality, on the number of specific vectors, and on certain other causes. In some instances the propagation of the infection may in itself be the cause of the extermination or extinction of the vectors and thus bring to an end the infection. So, for instance, intensive propagation of the plague may lead to the extinction of the susceptible animals, and with them the pathogen itself also perishes; as a result the site of infection disappears. The foci may be re-established when the area is again populated by potential reservoir hosts of the infection; if these animals contract the pathogen the infection may break out again among the human population.

The extensive propagation of endemic diseases with natural foci among humans causes the latter to become reservoir hosts to the infections. Rodents pass pneumonic plague to humans; the latter acquire the disease and become the principal vectors of epidemic pneumonic plague. Some transmissible infections evidently change their reservoir hosts in the process of evolution; dogs and certain wild animals are the reservoir hosts of both the Mediterranean and Central Asia forms of kala-azar (visceral leishmaniasis), but the disease may also be spread from human to human through the agency of sandflies. In India this infection emancipated from its animal reservoir over a period of many centuries, until man remained its sole reservoir.

Another example of such an evolution is yellow fever, a disease with natural endemic foci in tropical forests. However, when this disease is conveyed to urban communities in which the *Aedes aegypti* mosquito breeds abundantly epidemics of yellow fever appear, and the source of the infection is man.

Another thing to bear in mind is that all prerequisites for the development of the infection exist in certain localities, as the corresponding vector is present while the absence of man and animal reservoirs prevents the formation of an endemic site of the disease. Thus, on the Caucasian coast of the Black Sea the *Aedes aegypti* was formerly seen, but the absence of yellow fever among humans, monkeys, etc., made the appearance of the infection impossible.

Finally, another point to remember is that anti-epidemic measures, complete cure of all patients, extermination of animal reservoirs of the infection (infestation) and of the vectors or intermediaries may cause the disappearance of a transmissible endemic disease with natural foci in a given locality. Similar results may be attained by making changes in the environment. An illustration of this is the levelling of all the "houses" (step-wells) in Bukhara by L. M. Isayev; with the subsequent construction of a water mains dracunculosis (guinea worm) was completely exterminated in this city.

In establishing the scope of diseases to be included in this manual the authors have proceeded from specific native factors postulating the development in warm climates of endemic diseases with natural foci that are either associated with the presence of vectors, or appear in the human body under the effect of the hot climate and local dietary habits. In particular, dietary deficiency leads to the widespread incidence of various avitaminoses—sprue, beriberi, fermentative enterocolitis, and other diseases. The authors have considered it necessary to include in this manual also morbid conditions resulting from the bites of poisonous fauna common to tropical lands—snakes, black spiders, etc., and have also allotted some space to problems associated with the influence on the human body of heat and insolation factors (sunstroke and heatstroke, the drinking disease, etc.).

# MALARIA

---

Synonyms: malaria, febris intermittens (Lat.); Wechselfieber, Sumpfeieber (Germ.); paludisme, fièvre palustre (Fr.); intermittent fever, ague (Engl.); malaria, febbre malariche (Ital.); paludismo (Sp.).

## HISTORY

Malaria is one of the oldest of human ailments. Diseases resembling malaria are mentioned in the most ancient of literary monuments—the Chinese scrolls and Egyptian papyri.

Malaria was described most circumstantially in ancient Rome where it raged with greater violence than in all other countries of the European continent.

The Roman authors Varro and Columella (1st century B. C.) were the first to associate the propagation of malaria with swamps and mosquitoes.

According to Herodotus, feverish chills were widespread in the 5th century B. C. among the Scythians, ancient inhabitants of the South Russian plains.

The first written testimonial of malaria in old Slav literature is to be found in *Slovo Daniila Zatochnika* (*Word of Daniel Zatochnik*), a most interesting literary monument of the 12th century.

The famous Armenian physician Mhitar Geratzi compiled a treatise *About Fevers* (1184) in which he described the characteristic course of malaria as he observed it in Cilicia and Armenia.

*Russkiye vrachebniki* (*Russian Medical Lore*), a book written by L. Zmeyer, contains historical data on malaria taken from a medical script of the 16th century.

Mention of “three- and four-day internal fever” in the army may be found in a medical manual written in 1708 by Daniil Turchin, called *Apteka obozovaya, ili sluzhivaya* (*Pharmacy in Military Trains*).



The spread of malaria among military troops and the population at large caused Peter I to issue an edict on the import of quinine into Russia.

Consequently, malaria was in the past and is even at present one of the most widespread and truly "historical" diseases on earth.

The first milestone in the history of malaria discoveries was laid in 1640, when the physician Don Juan de Vega successfully employed a decoction of cinchona bark in treating Countess Chinchon, the wife of the vice-consul of Peru, for malaria.

In 1648, cinchona bark was introduced on a wide scale for the treatment of malaria in Spain and in a number of European countries.

In 1696, Richard Morton in his work entitled *Pyretologiae opera medica* presented the first clinical description of malaria and substantiated the therapeutic effect of cinchona bark.

In 1717, Lancisi connected the spread of malaria with the harmful influence of swamps and marshes.

In 1723, the English physician Thomas Sudenham described intermittent, monothermic, estival and autumnal fevers separately and published data on the successful treatment of malaria with cinchona bark.

In 1721, Torti, in a treatise on malignant malaria, gave a classic description of the severe forms of this disease.

In 1816, the Russian investigator F. I. Gizeh first obtained quinine in crystalline form. Four years later (1820) the French chemists Pierre Joseph Pelletier and Joseph Bienaime Caventou succeeded in isolating the pure quinine alkaloid.

The isolation of the crystalline form of quinine was conducive to a significant expansion and rationalisation of malaria therapy.

Most prominent in promoting the widescale popularisation of quinine in the first quarter of the 19th century in Russia and in evolving an expedient course of treatment were I. S. Minervin (field doctor to the Caucasian corps) and A. A. Charukovsky (an army doctor).

In 1879, A. M. Butlerov and A. N. Vishnegradsky isolated pure quinoline from cinchonine and methoxquinoline from quinine. In 1879, V. I. Afanasyev described the pathoanatomic aspect of comatose malaria; this investigator correctly interpreted the parasitic nature of the pigment bodies he observed.

On November 6, 1880, the French army physician Charles Louis Alphonse Laveran discovered the pathogen of malaria, described its morphology in detail, and proved that it was an animal microorganism.

In 1885, V. Y. Danilevsky discovered avian malaria. In 1885, Ettore Marchiafava and Angelo Celli described the morphology and development of the malaria parasite, the *Plasmodium*, which they observed in preparations stained with methylene blue.

In 1889, N. A. Sakharov published the first comprehensive description of the pathogen of malignant malaria, *P. falciparum*; in 1894, this author described the flagellate bodies as being phases in the development of the malarial plasmodia. In 1891, D. L. Romanovsky instituted a panchroma-

tic method for staining the plasmodia with methylene blue and eosin, the forerunner of subsequent azure-eosin stains of the Giemsa type.

In 1897, Ronald Ross discovered the vector of malaria, the *Anopheles* mosquito, and subsequently described all the sporogony stages in the mosquito.

In 1898-99, the famous Italian physicians and naturalists Bastianelli, Bignami and Grassi confirmed all the stages of sporogony in the *Anopheles* in experiments with mosquitoes fed on malaria patients.

In 1921, Prof. Y. I. Martzinovsky founded the Tropical Institute in Moscow.

In 1924, Y. N. Pavlovsky and A. Stackelberg instituted a permanent committee for the study of malarial mosquitoes, under the auspices of the Zoology Institute of the Academy of Sciences of the U.S.S.R.

In 1926, the German researchers Schuleman, Schönhofer and Wingler succeeded in synthesising plasmochin. Shortly afterwards the Soviet chemists O. Y. Magidson, I. T. Strukov, G. V. Chelintsev and I. L. Knunyants synthesised plasmocid.

In 1930, Mitzsch, Mauss, and Hecht obtained atabrin (atabrine dihydrochloride), and in 1933, I. L. Knunyants, G. V. Chelintsev, A. M. Grigoryevsky and Z. V. Benevolenskaya synthesised acrichin [quinacrine (mepacrine) hydrochloride].

In 1947, British scientists obtained paludrine, synthesised in the Soviet Union under the name of bigumal (by A. F. Bekhli, V. A. Ufimtsev, et al.).

In 1952, a preparation called quinocide was synthesised in the Soviet Union (by V. D. Stavrovskaya and M. B. Braude), closely resembling the primaquine synthesised by Elderfield.

During the years 1930 through 1958 Soviet scientists headed the drive against malaria and succeeded in practically eradicating it in the U.S.S.R. as a mass disease.

## ETIOLOGIC AGENTS OF MALARIA

The causative agent of malaria belongs to the phylum *Protozoa*, class *Sporozoa*, order *Haemosporidiae*, family *Plasmodiidae*, genus *Plasmodium*.

It is at present accepted that there exist four species of the malaria parasites: *Plasmodium vivax* (Grassi a. Feletti, 1890); *Plasmodium malariae* (Laveran, 1881); *Plasmodium falciparum* (Welch, 1897); *Plasmodium ovale* (Stephens, 1922) (Fig. 1).

To complete the picture it should be pointed out that man can be infected by the parasite that causes malaria in monkeys. These parasites include: *Plasmodium knowlesi*, evoking daily paroxysms in man; *Plasmodium inui*, causing paroxysms over 72-hour intervals in monkeys; *Plasmodium rodhaini* (discovered in the chimpanzee), very like *Plasmodium malariae*. Mosquito vectors transmit *Plasmodium cynomolgi* var *bastianelli* to man.

Besides the above species, monkeys have also been observed to be affected by *Plasmodium brasilianum* (72-hour cycle); *Plasmodium reiche-*

*nowi*, the gametocytes of which resemble those of *Plasmodium falciparum*, *Plasmodium cynomolgi*, and *Plasmodium schwetzi*, similar to *Plasmodium vivax*.

### **Development of the malaria plasmodia in the human body (schizogony cycle)**

The malaria parasite enters the human body with the bite of an infested *Anopheles* mosquito.

The sporozoites of the parasite are introduced into the blood stream with the saliva of the *Anopheles*; these sporozoites are formed as a result of the development and multiplication of the parasite in the mosquito. It was formerly considered that the sporozoite penetrates directly into the erythrocyte, where it turns into a merozoite. Observations of such penetration were published in 1903 by Schaudinn. However, no subsequent investigators could confirm these observations. Thus the questions of what happens to the sporozoites after they penetrate into the human body, and of where they go during the protracted incubation period remained obscure. Moreover, the blood of the patient is not infectious throughout this period, direct proof of the absence of the plasmodia in the erythrocytes. It was also not clear where the plasmodia kept themselves during the latent winter season. Circumstantial proof of the existence of peculiar tissue phases of the plasmodia is also derived from the different reactions of malaria plasmodia to various chemical preparations.

1. *Tissue stages, tissue parasites, or exoerythrocytic stages of the malaria plasmodia.* At present the developmental cycle of the malaria plasmodia is held to be as follows.

The sporozoites penetrate into the human body with the saliva of the mosquito; through the blood stream they migrate to the liver, where they infest the hepatic cells and pass through a pre-erythrocytic cycle of development, of variant duration in the different species. In the hepatic cells the parasites become rounded, the mass of their cytoplasm increases; there is one nucleus. This is the non-pigmented schizont stage. Further the schizont grows and multiple division of the nucleus occurs (by the end of the divisional phase there are as many as 800-1000 nuclei). The parasite grows to 45 and even more microns. In the cytoplasm the nucleus turns into irregular lumps that show red with the Romanovsky stain, while the cytoplasm stains a light blue. In the next stage of development the cytoplasm also splits and the large bodies divide into a great number of small merozoites. The first generations of the tissue phases in the development of the sporozoites are called cryptozoites, and they divide into a form called cryptomerozoites. The cryptomerozoites of *Plasmodium falciparum* gain access to the erythrocytes, laying the foundation of the erythrocytic cycle of development.

Much more complicated is the development of *P. vivax*, *P. malariae*, and *P. ovale*. Part of their cryptomerozoites penetrate into the red blood cells, while the other part enters new liver cells to continue the tissue cycle.

Within this latter cycle forms periodically appear that are capable of gaining access to the blood, thus conditioning the possibility of relapses of the disease.

The recurrent emergence into the blood of the remaining exoerythrocytic forms of the parasite are the cause of the onset of relapses.

It must be remembered that the development of the parasites in the tissue cells calls forth no reaction in the organism. Herein lies the explanation of the asymptomatic incubation period and of the interludes between the paroxysms of malaria.

2. The *merozoite*. The merozoite consists of a small clot of cytoplasm with one cherry-red nucleus. The diameter of the merozoite is  $1-2\mu$ . Some merozoitic generations turn into the asexual forms of the parasite, others into the sexual forms, the gametes, the further development of which is possible only in the body of the *Anopheles* (sporogony).

3. *Ring-form stage* (the “ring”). Upon gaining access to the erythrocyte the merozoite starts growing, and a vacuole appears in its cytoplasm. At this stage the malaria parasite resembles a ring with a “ruby” (the nucleus) mounted in its thicker part.

4. *Ameboid schizont*. *Semimature schizont*. As the parasite grows its cytoplasm increases, and its contours become irregular—the plasm projects pseudopodia; pigment appears in the cytoplasm; this pigment is the product of the splitting of hemoglobin effected by the parasite.

5. The *mature schizont* (morula). By the time of its complete maturation the schizont pulls in its pseudopodia, becomes rounded and occupies almost the entire erythrocyte. The division of the nucleus into multiple nucleoli is attended by a division of the cytoplasm into separate areas concentrated around each nucleolus.

The number of merozoites in the morula differs from 6 to 24, depending on the species of the parasite. The pigment grains gather into one compact clump.

When the morula falls apart the erythrocyte is destroyed, and the merozoites are liberated into the blood plasma. Here they again penetrate into the red blood cells, but a great number of them are destroyed, owing to the formation of a temporary immunity (if this did not happen all the patient's erythrocytes would be infected with the malaria parasite in several cycles of schizogony).

The development of the malaria parasite in the erythrocyte takes 48 hours in *P. vivax*, *P. ovale* and *P. falciparum*, while in *P. malariae* it is 72 hours.

*Gametocytes*. *Gametes*. The first term is widely used for designating the sexual stages of the malaria parasites circulating in man's blood.

A gamete is a sex cell capable of participating in the process of fertilisation. The male gametocytes in the human blood are incapable of fertilising and their transformation into mature gametes occurs only in the body of the mosquito; the female gametocytes in the human blood are gametes.

The gametocytes of all the species of the malaria plasmodium, except *P. falciparum*, are found in the peripheral blood at all stages of their

development. In falciparum malaria the erythrocytes in which the development of the gametocytes has commenced are detained in the vessels of the viscera and subcutaneous tissue until complete maturation of the gametocytes occurs; it is only in very heavy infections with *P. falciparum* that the young gametocytes are found in the peripheral blood.

In the human body the gametocytes are incapable of further development, and they gradually disintegrate. Further development can only take place in the body of the *Anopheles* mosquito.

### Development of the malaria plasmodia in the mosquito (sporogony cycle)

The malaria parasite passes its sexual cycle of development in the bodies of *Anopheles* mosquitoes. The mature male and female gametocytes taken up from human blood by the mosquito are liberated from the

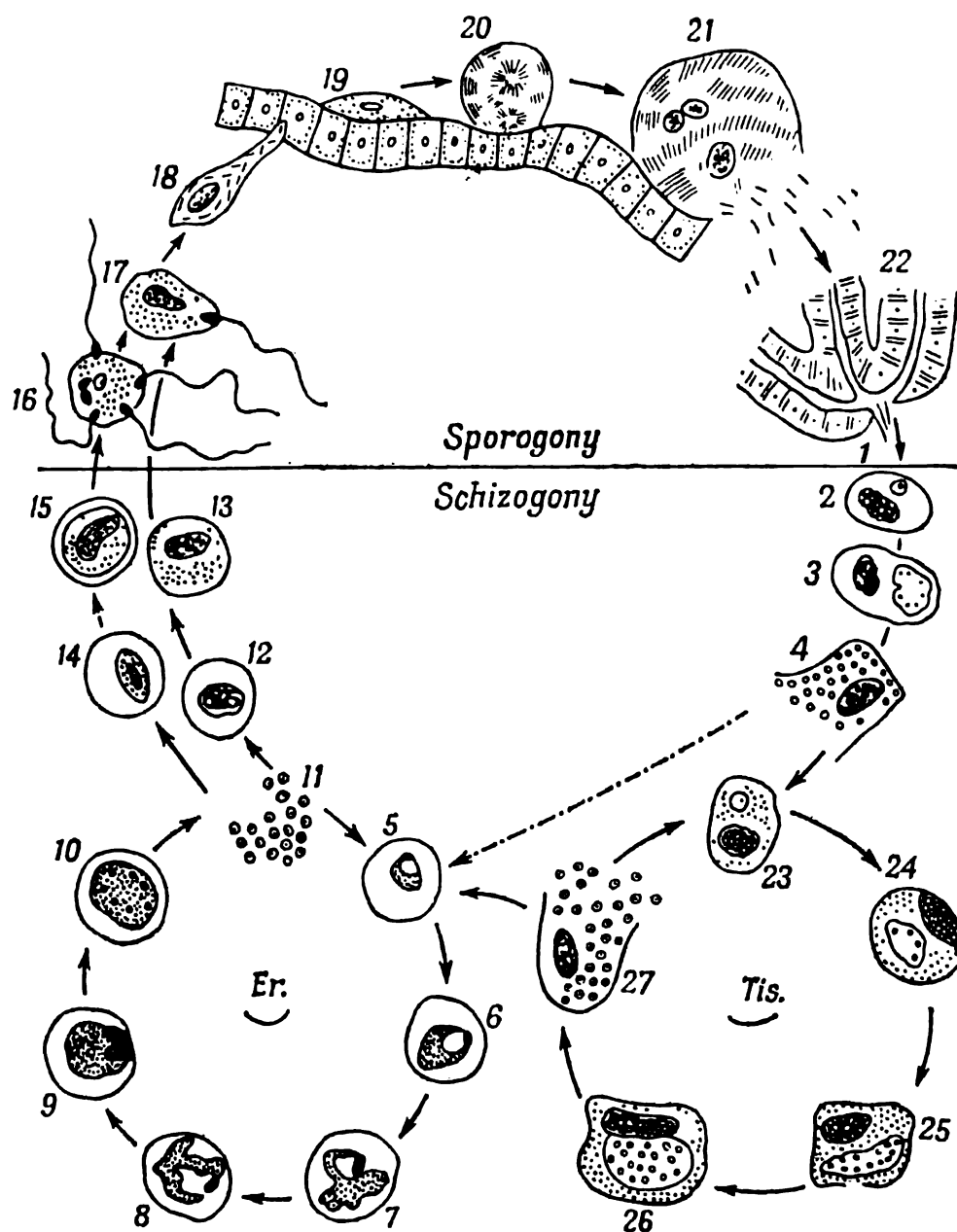


Fig. 2. Developmental cycle of malaria parasite (schematic)

1—emergence of sporozoite from the salivary gland and its penetration into a hepatic cell; 2-4—pre-erythrocytic cycle; 5-11—erythrocytic schizogony; 12-13—development of female gametocyte; 14-15—development of male gametocyte; 16—formation of microgametes; 17—fertilisation; 18—penetration of zygote through wall of mosquito stomach; 19-20—development of cyst; 21—mature cyst ruptures and sporozoites emerge; 22—sporozoites in the salivary gland; 23-27—development of subsequent tissue generations of the parasite in the hepatic cells (does not occur in *P. falciparum*)

erythrocyte and then commence their gametocytic or sexual cycle of development; the schizonts extracted with the human blood by the mosquito are simply digested in its stomach.

The male gametocyte expels 4-8 hairlike flagella containing nucleic substance. Moving around in the stomach of the mosquito these gametocytes meet with female sex cells (macrogametocytes) which they fertilise.

The fertilised cell—the zygote (or oökinete)—is at first rounded or ovoid, then it gradually elongates, becoming vermiform (15 microns long and 2 microns wide). The motile zygote bores through the inner layer of cells lining the mosquito's stomach and stops under the outer (serous) layer. Here it becomes spherical and encysts, turning into an oöcyst (6-8 microns).

About two days are needed from the time the mosquito ingests the blood to the appearance of the oöcysts (the process develops at a temperature of 25°C). The contents of the cyst divide repeatedly, and sporozoites are formed in it; the cyst grows to 50-60 microns. The number of sporozoites reaches several thousand in one cell, while the number of cysts depends on the saturation of the patient's blood with gametocytes. This number ranges from solitary individuals to five hundred.

The mature cyst breaks open and the thousands of sporozoites are distributed by the hemolymph over the entire body of the mosquito, but settle predominantly in the salivary glands. When the mosquito pricks the human skin to withdraw blood it conveys a certain amount of sporozoites into its victim's body; the subsequent bites of the insect are likewise infectious (Fig. 2).

### **Susceptibility of anopheles to infestation and duration of sporogony**

Not all the gametocytes are capable of infesting the mosquito. Part of them are dying off and therefore are incapable of further development. The sporogony cycle is affected by many circumstances. If the atmospheric temperature falls below 16 °C directly after the mosquito has ingested infested blood the sporogony cycle cannot be completed. If the mosquito is in a low-temperature environment (slightly lower than 16°) for only a short time and the temperature soon rises, the cycle proceeds to its end.

After the cysts have been formed in the intestinal wall of the mosquito marked drops in the surrounding temperature check the development of the parasites, but do not always destroy them. This depends on the length of time the mosquito is exposed to the low temperature and on the specific features of the parasites: *P. falciparum* cysts are more sensitive to cold than are *P. vivax* cysts.

Higher environmental temperatures are conducive to acceleration of the process of sporogony and to the formation of a greater number of cysts (consequently, to the production of more sporozoites), and also to a more intensive bloodsucking activity (humans are attacked by the mosquitoes more frequently).

Table 1

Duration of Sporogony (in Days) at Various Constant Temperatures in the Different Species of the Parasite

Species	Temperature													
	16-17°	17-18°	18-19°	19-20°	20°	21-22°	22-23°	24°	25°	26°	27°	28°	29°	30°
<i>P. vivax</i> .....	45	32	26	22	19	16	13	11	10	9	8	7	6.5	6.5
<i>P. falciparum</i> .....	—	—	—	26	—	20	16	14	12	11	10	9	8	8
<i>P. malariae</i> .....	—	—	—	—	—	—	—	18	16	—	—	—	—	—

Note: This table was compiled on the basis of data obtained in experimental infections. A dash signifies that no experiments were carried out.

Table 2

Differential Diagnosis of Malaria Parasites (Based Principally on Data of S. D. Moshkovsky)

	Parasite				
	<i>P. vivax</i>	<i>P. malariae</i>	<i>P. falciparum</i>	<i>P. ovale</i>	
	2	3	4	5	
Type of malaria	Tertian	Quartan	Malignant tertian	Tertian	
Duration of schizogony	48 hours	72 hours	48 hours	48 hours	
Stages of the parasite found in the peripheral blood	All schizogony stages and gametocytes	All schizogony stages and gametocytes	Usually only rings and mature gametocytes. In very heavy infections all other schizogony stages as well	All schizogony stages and gametocytes	

Young schizonts (ring forms)	The ring forms occupy $\frac{1}{3}$ to $\frac{1}{4}$ of the erythrocyte	As in <i>P. vivax</i>	Small, fine rings occupy about $\frac{1}{6}$ of the erythrocyte diameter; the larger ones take up as much as $\frac{1}{3}$ of the erythrocyte diameter; the nucleus is frequently divided in two. One erythrocyte may often contain several rings (as a rule these forms alone are found in the peripheral blood)	Size and form as in <i>P. vivax</i> and <i>P. malariae</i> , but with a larger nucleus
Ameboid schizonts	Occupy over $\frac{1}{3}$ of the erythrocyte diameter. The pseudopodia are well-defined. Pigment distribution is uniform in the young schizonts; as the parasite matures the pigment concentrates in clumps	<p>a) The same as in <i>P. vivax</i>, of differing size depending on degree of maturation of schizont. Pseudopodia are wide, not clearly definable.</p> <p>b) Band-like schizonts; the parasite lies on the equator of the erythrocyte, like a band, its nucleus is stretched out along one edge. The pigment in the ameboid schizonts is distributed as in <i>P. vivax</i>; in the band form it lies along one edge, opposite the nucleus</p>	Weakly expressed ameboid form. In the early stages the pigment already accumulates in a dense clump. Commonly not found in the peripheral blood	Resemble the <i>P. malariae</i> schizonts, but larger. Distribution of pigment as in the ameboid schizonts of <i>P. vivax</i> and <i>P. malariae</i>



Table 2 (continued)

	Parasite			
	<i>P. vivax</i>	<i>P. malariae</i>	<i>P. falciparum</i>	<i>P. ovale</i>
1	2	3	4	5
Morula	12-18 merozoites arranged randomly around the pigment clumps	6-12 merozoites forming a regular rosette on the periphery of the pigment mass	12-24 (usually 16) merozoites, smaller than in the other species; the merozoites are arranged at random around the clumped mass of pigment	8, rarer 10-12 merozoites arranged randomly around the clumped mass of pigment
Gametocytes	<p>Enlarged round or ovoid cells with no pseudopodia, occupying almost the entire enlarged erythrocyte.</p> <p>The pigment is coarser than in the schizonts and is distributed uniformly.</p> <p>The female gametocytes are slightly larger than the male, their nucleus is smaller than in the male gametocytes, the cytoplasm stains more intensively</p>	<p>The same as in <i>P. vivax</i>, but smaller, not exceeding the size of a normal erythrocyte</p>	<p>Crescent-shaped. The pigment in the female gametocytes adheres closely to the nucleus; the latter is in the centre of the parasite. The ends of the body taper slightly.</p> <p>In the male gametocytes the pigment is dispersed over a wide area around the nucleus which occupies over half the length of the gametocyte. The ends of the body are rounded</p>	

Infested erythrocytes	Grow with the development of the parasite. Fine purplish-red Schüffner's dots appear in abundance. The erythrocytes are predominantly deformed and hypochromic	Do not change nor grow, nor are they hypochromic	Are not enlarged or hypochromic. When treated with a stain dissolved in alkaline water the erythrocytes containing the ring forms of the parasite are seen to contain 3-5 purplish-red grains, Maurer's dots. The erythrocytes containing the developing gametocytes display the large grains of Argutinsky, or thread-like bodies curled in loops or figures of eight	Enlarged, hypochromic; some erythrocytes containing half-grown schizonts become ovoid or acquire a fringe. Grains resembling Schüffner's dots are present, but they are larger and not so numerous
-----------------------	--	--	--	--

The computations performed by S. D. Moshkovsky showed that in order to complete the sporogony cycle each species of the parasite is in need of a definite cumulative amount of warmth.

This point was well illustrated by the investigations of B. P. Nikolayev, whose results are drawn up in Table 1.

It has at present been established that the development of the *P. vivax* in the *Anopheles* mosquito at 16-17 °C takes approximately 45 to 55 days, at 19-20° 22 days are needed, and at 25° — 10 days. The shortest period of development is 6-7 days at a temperature of 28-30 °C.

The development of *P. falciparum* in the vector begins at 17-18°C. The maturation of its sporozoites calls for a longer term than in *P. vivax*; for *P. falciparum* this period is 26 days at 19-20°, 12 days at 25°, and 8 days at 30°C.

The sporogony of *P. malariae* commences at the same temperature as in *P. falciparum*, and requires still longer periods (16 days at 25°).

Conditions for sporogony and the development of the gametocytes are not always uniform in the body of the mosquito. The opportunity for the latter to become infested depends on the adaptiveness of the given strain of the parasite to the mosquitoes of a given species or geographical variety. Thus, for instance, the *A. maculipennis* mosquitoes from Great Britain become infested with the *P. falciparum* widespread in Italy, but are immune to the *P. falciparum* varieties common to Central Africa or India.

At times infestation only occurs after repeated ingestions of infested blood. In the autumn certain species of *Anopheles* mosquitoes are less susceptible to infestation than others.

Some species of the mosquito in the southern areas of the European part of the U. S. S. R., in Central Asia and the Transcaucasus are capable of infecting people throughout the autumn and even in the winter. *A. superpictus* and *A. maculipennis atroparvus* are two such species. They continue their bloodsucking activities in the late autumn, but their ovaries do not develop any longer.

As these mosquitoes do not fly out of closed premises to find water for oviposition they are particularly dangerous for human beings.

Table 2 is a diagnostic aid for classifying the species of malaria parasites.

### Malaria parasites in thick smears

In laboratory practice the diagnosis of the parasite is commonly established by examination of thick smears, therefore we shall dwell briefly on the morphological aspects of the malaria parasites in these preparations.

*P. vivax*. The majority of the rings do not retain their form; they are slightly ruptured, and a round or elongated clot of plasmodium lies adjacent to the small nucleus. The cytoplasm of the ameboid schizonts is also often disrupted, several clots are grouped around the nucleus. The mature schizont is definable by 12-18 merozoites arranged around a clump of

pigment grains; occasionally some merozoites may lie separately. Sometimes the parasite is seen in an erythrocyte, the pale disk of which has been retained.

*P. malariae*. The rings are mostly ruptured. The ameboid and band-form schizonts are round or oval. The mature schizont is easily recognised by the characteristic arrangement of its 6-12 merozoites around a central golden-yellow clump of pigment.

The gametocytes are distinguished from the schizonts with difficulty. The erythrocytes are usually completely lixiviated.

*P. falciparum*. In a successfully stained thick smear very small rings with red nuclei may sometimes be observed; part of these rings are ruptured, their light blue cytoplasm and nucleus resemble an exclamation mark. No red blood cell remnants are visible. The gametocytes are well represented; they are recognisable by their characteristic cucumber or sausage form (Fig. 3).

#### ANOPHELES MOSQUITOES, THEIR PROPAGATION AND ROLE IN THE TRANSMISSION OF MALARIA

*The vectors of the malaria infection (the malaria parasites) are mosquitoes of the genus Anopheles.*

There are over 150 known species of this genus on earth, more than 50 of which are epidemiologic factors.

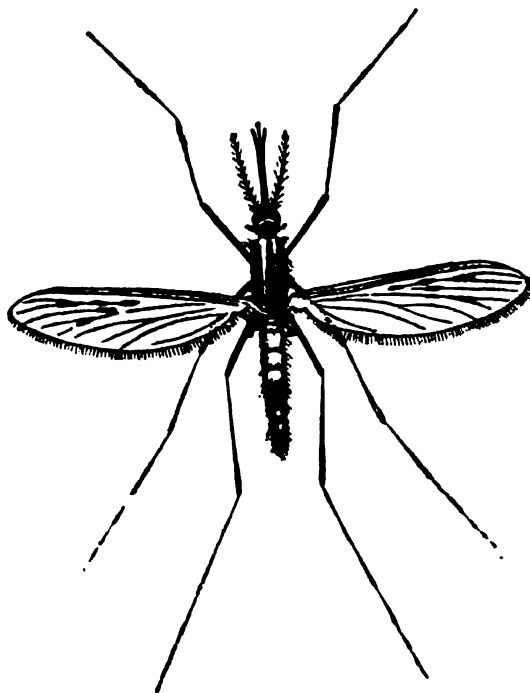


Fig. 4. *Anopheles maculipennis* (female)

In the U. S. S. R. nine species of *Anopheles* are found; the active vectors of malaria among them are *Anopheles maculipennis* (Fig. 4) (of the known seven subspecies the following are encountered in the U.S.S.R.: *A. m. messeae*, *A. m. typicus*, *A. m. atroparvus*, *A. m. melanoon*, *A. m. subalpinus*, and *A. m. sacharovi*), *A. superpictus*, *A. pulcherrimus*. Less

active vectors are *A. bifurcatus*, *A. hyrcanus*, *A. plumbeus*. The species *A. algeriensis*, *A. lindesayi*, and *A. marteri* take no noticeable part in epidemics.

*A. maculipennis* is the most widespread species (it is absent only in the Far East). This is the most important vector of malaria, its different subspecies are found in the various latitudes and areas of the U.S.S.R.

*A. superpictus* habitates the Black Sea and Caspian coasts of the Caucasus and in Central Asia, it is found predominantly at the foothills. Its larvae develop in shallow pools formed in pebbly river beds.

*A. pulcherrimus* ("beauteous", "silvery" mosquito) is common to Central Asia and the eastern Transcaucasus. It breeds in large bodies of stagnant water.

*A. bifurcatus* is found in the European part of the U.S.S.R., Western Siberia, the Caucasus, and Central Asia. It populates pools around springs. This is not a numerous species and it does not molest man much.

*A. hyrcanus* is found in the Far East (the Ussuriisk territory, along the entire stretch of the Amur river), as well as in the Altai Mountains, the estuaries of the Ural and Volga rivers, southern Ukraine, Moldavia, Central Asia, the Caucasus. For breeding it selects flood valleys, deltas, backwaters, rice fields. This wild species has relatively little to do with man, therefore its epidemiologic significance is negligible.

*A. plumbeus* is common to the Caucasus, both the mountains and the Black Sea coast, to southern Ukraine and Moldavia. Its larvae live in tree hollows. The insect hibernates in its larval stage.

*Principal vectors of malaria.* Western Europe: *A. maculipennis messeae*, *A. maculipennis labbranchiae*, *A. maculipennis sacharovi*, *A. superpictus*.

North Africa and the Near East: *A. maculipennis labbranchiae*, *A. maculipennis sacharovi*, *A. superpictus*, *A. bifurcatus*, *A. multicolor*, *A. sergenti*, *A. pharoensis*.

Central and South Africa: *A. gambiae*, *A. funestus*, *A. hargreavesi*, *A. pharoensis*, *A. moucheti*, *A. pretoriensis*, *A. nili*, and others.

India, Ceylon, the peninsula of Indo-China, Burma, the Sunda Isles, South China: *A. minimus*, *A. culicifacies*, *A. stephensi*, *A. superpictus*, *A. fluviatilis*, *A. maculatus*, *A. sundaicus*, *A. subpictus*, *A. philippinensis*, *A. annularis*, *A. umbrosus*, *A. varuna*, *A. kochi*, *A. barbirostris*, *A. aconitus*, *A. leicosphyrus*, *A. hyrcanus nigerrimus*. *A. hyrcanus* and *A. minimus* are mostly found in China.

The Philippines: *A. minimus flavirostris*, *A. mangianus*.

Australia, New Guinea: *A. punctulatus*, *A. bancrofti*, *A. annulipes*.

North America: *A. quadrimaculatus*, *A. maculipennis freeborni*, *A. walkeri*.

Central America: *A. albimanus*, *A. bellator*, *A. pseudopunctipennis*, *A. darlingi*, *A. aquasalis*.

## Essential biological features of malaria mosquitoes

Upon emerging from their pupae the males and females copulate near water. The fertilised females search out humans or domestic animals to extract blood from (the ova can only develop when the insect feeds on blood). The males do not suck blood, and they soon perish.

The females satiate themselves with blood in closed premises and usually remain in these premises until the blood has been digested and the ovaries have ripened; this process takes two days at 30°, four days at 20°, and seven at 15°C.

Malaria mosquitoes are usually inactive in the daytime and do not molest people. But in the evening and at night the hungry females swarm into closed premises in search of blood; in warm weather they bite in the open, too.

When the ova have ripened the females swarm from their "hunting grounds" to water reservoirs for oviposition. The complex cycle of processes beginning with the ingestion of food and ending with oviposition comprises the gonadotrophic cycle of the female mosquito. Every female mosquito may go through several such cycles during its lifetime.

The entire cycle from fertilisation, development of the ovum, larva and pupa to the winged mosquito takes from 2 to 4 weeks.

At a mean daily temperature of 16 °C *A. maculipennis* develops in 30 days, at 20-22°, in 18 days and at 24-27° in 14 days.

Consequently, a malaria mosquito may produce as many as eight generations during one season in torrid zones. It is perfectly clear that in such geographic areas, in the presence of adequate water bodies and blood reservoirs, the malaria mosquitoes can breed in verily astronomic numbers.

At the beginning of the autumn the so-called diapause occurs in the female malaria mosquito (cessation of the development of the ovaries).

In the central European belt such females no longer extract blood. They feed on carbohydrates and accumulate fat for the winter. The hibernating females remain in a torpid state in cold premises such as cellars or attics.

In the spring they awaken and fly out for the first time (in Uzbekistan this occurs February 10-20 in the case of *A. maculipennis*, while *A. superpictus* only awakens March 10-20).

Multitudinous swarming takes place two-three weeks later. The ova are found in water reservoirs shortly afterwards.

In the southern areas mass breeding of the first generation of mosquitoes is usually observed in the middle of May or at the end of the month, in the temperate belt in June (oscillations in these periods are associated with atmospheric conditions — temperature of air and water).

## Season of malarial infestation of man

The transmission of malaria and the appearance of malarial infections are seasonal occurrences, except for a number of equatorial localities where the seasons of the year hardly differ and transmission of malaria occurs the year round.

The epidemic season, when man acquires the infection, is of various duration, depending on atmospheric conditions and the species of *Anopheles* mosquito.

The length of the epidemic season differs, even with one and the same vector, in the different topographical and geographical zones. For instance, in the temperate belt *A. maculipennis messeae* is common to, this season lasts for two to two-and-a-half months, while its duration in the south may be as long as 4 or 5 months.

In the central belt effective infestation of the mosquitoes occurs in May or at the beginning of June; man can be infected in June and the beginning of July. In September the mosquitoes hide for the winter, and the last sporadic transmissions of infection to man may occur in September. The epidemic season is 2-3 months long.

In the zone of propagation of *A. superpictus*, for instance, in the Uzbek and Tajik Republics, effective infestation of the mosquitoes may occur toward the end of April and in May, people become infected in May and June, the season ends in September-October. Thus the malaria season in these areas lasts 4 to 6 months. In Uzbekistan the epidemic season of infection by *A. maculipennis*, in the zone it is common to, opens in May.

In the areas of propagation of *A. maculipennis atroparvus* opportunities for infection with malaria may be protracted to the beginning of the winter, as this subspecies repeatedly extracts blood even in the autumn and winter.

In the central belt of the Russian Federation, where the principal vector is *A. maculipennis messeae*, infection with malaria takes place in the third quarter of the year, in the southern belt—in the second and third quarters.

In the temperate latitudes the season of mass malaria morbidity begins in the spring, shortly before the mosquitoes fly out of their winter quarters (throughout March and April, differing with locality, latitudes and climate).

These spring outbreaks of the disease are caused by the following factors: 1) late relapses of last year's malaria and 2) primary paroxysms in persons infected during the preceding season with a strain of *P. vivax* (so-called northern strain) that has a prolonged incubation period. Fresh cases of tertian malaria with short incubation periods (the southern strain of *P. vivax*) appear in July-September. In more southern regions a wave of malignant malaria superimposes itself on the latter, and later on quartan malaria, too.

However, it must be pointed out that in some warm countries the seasons of contraction of malaria and of the outbreak of paroxysms of the

disease are more prolonged, while in certain zones, as, for instance, in tropical Africa, malaria infection and paroxysms occur throughout the year.

**GEOGRAPHICAL DISTRIBUTION OF MALARIA**

The boundaries of possible propagation of malaria are between 63° N. lat. and 30° S. lat. in the Eastern hemisphere, and 40° N. lat. and 40° S. lat. in the Western hemisphere. In certain areas of the Northern hemisphere malaria may spread to even higher latitudes (Fig. 5).

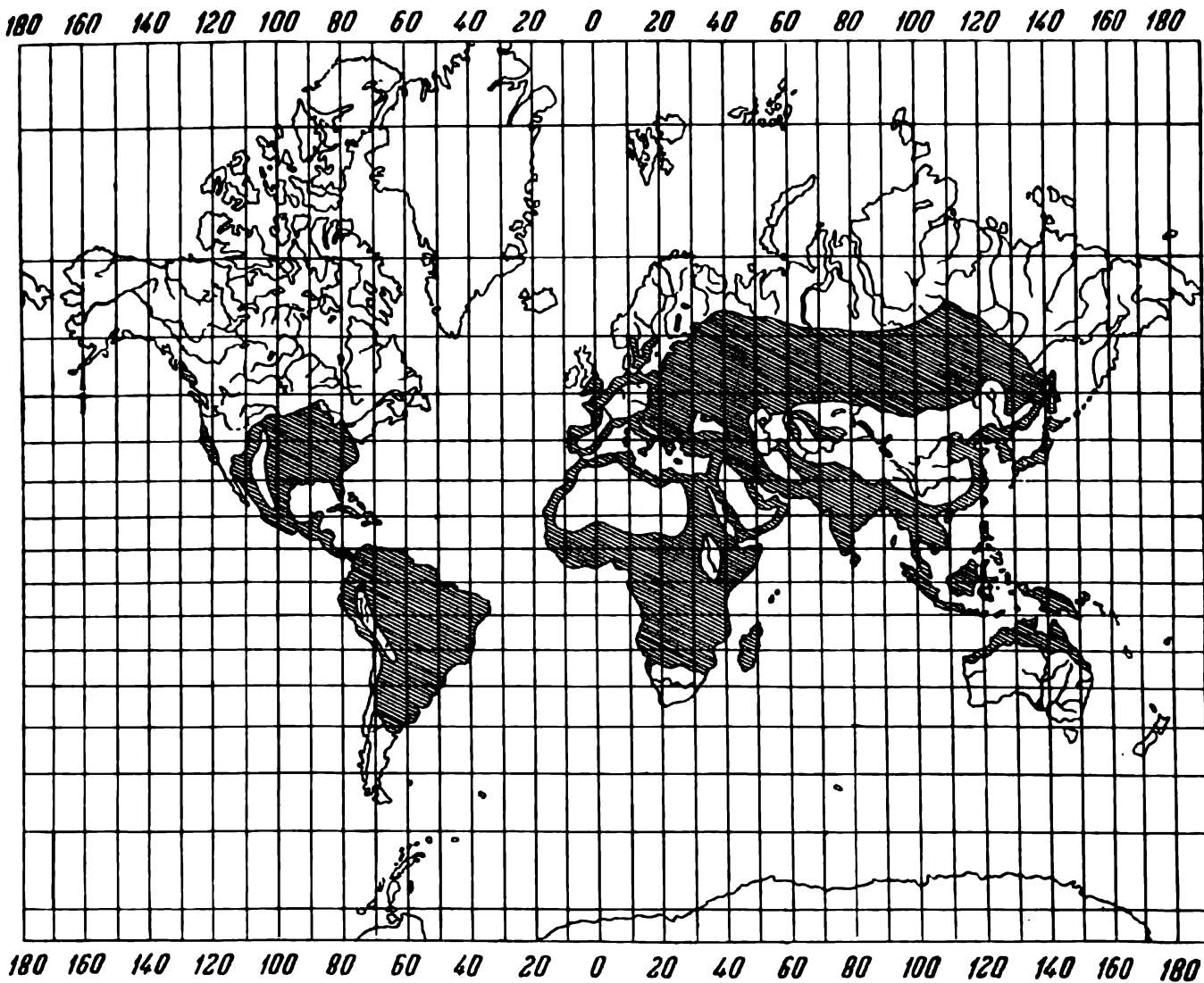


Fig. 5. Geographical distribution of malaria at the close of the first quarter of the 20th century (S. D. Moshkovsky and M. G. Rashina)

In prerevolutionary Russia malaria was one of the most widespread diseases.

This disease was particularly violent during the Civil War period, when the young Soviet Republic, fighting against the whiteguards and interventionists, was placed in an extremely difficult position.

After the October Revolution a state-planned campaign against malaria was instituted on an extensive scale; this campaign met with outstanding success. Malaria has practically been eradicated in recent years.



However, it still remains one of the most widespread diseases on earth. According to the incomplete data of WHO (the World Health Organisation under UNO), up to 100 million malaria patients are registered annually in all the countries of the world. In the recent past this figure was twice as large.

Thus, in Italy in the twenties and thirties of the present century 250,000 cases of malaria were registered among the 45 million population. During the war years, including 1945, the number of cases was approximately 133,842; however, thanks to a planned, intensive antimalaria drive the number of patients did not exceed 19,462 by 1949.

Signal achievements in the drive against malaria were attained in Greece, which formerly occupied one of the leading places in Europe in malaria morbidity; the number of patients in this small country was one million at the beginning of the present century. An intensive outbreak of malaria occurred in Greece during World War II (child mortality was very high, total mortality — up to 8,000 cases annually); thanks to a well-organised campaign the number of malaria cases was brought down to 15,000 by 1950.

One of the European countries distinguished for high malaria morbidity until the recent past was Rumania, where the number of cases in 1948 was 338,198. After the establishment of popular democratic power an intensive battle was launched against this disease: extensive hydrotechnical works were carried out, millions of square metres of land in the most malaria-ridden areas were treated with insecticides (Jassy, Tulcea). The results of all these measures were not long in displaying themselves: in 1956 the number of confirmed cases of malaria was brought down to 198.

Just as remarkable results were attained in Bulgaria, a country that numbered up to 130,000 malaria patients as recently as 1942; by 1956 this figure had decreased to merely 261 cases.

Malaria was formerly extremely widespread in Yugoslavia; one-third of the population (up to 5 million people) lived in malarial localities. In 1938 over 250,000 cases were registered, but in 1956 the number of patients did not exceed 800.

In Turkey malaria was a most widespread disease; 1,672,000 cases were registered in 1948. The measures undertaken for gaining control of this scourge brought the number of patients down to 54,000 by 1953.

Malaria is still a formidable disease in the countries of the Near East and Middle Asia — Syria, Iraq, Afghanistan; however, no reliable statistics on these countries are available.

Syria and Iran have launched an organised drive against malaria; in the former country 96,796 malaria patients have been registered instead of the 150,000 annual cases noted in the 1940-50 period.

The countries where malaria is most violent are India, Pakistan, and Ceylon. Forty-nine species and nine races of *Anopheles* are common to these lands, seven of these species are the basic vectors of malaria. As there is still no total registration of malaria in these countries data on its propagation are far from complete or precise. Reports by Singh state that ap-

proximately 800,000 annual deaths in India are due to malaria. At present an organised antimalaria campaign has been launched in many regions of India; over 200 special antimalaria expeditions have been organised.

Burma, a country directly adjacent to India, is also subject to malaria infection on a wide scale, but no precise data are available. Up to 7.5 million of the population inhabit malarial localities; morbidity is very high.

Twenty-four species of *Anopheles* have been registered in China. A centralised antimalaria drive has been organised in this country, dozens of malaria stations have been founded, and a decrease in morbidity has been observed in many areas (1956-57).

High malaria rates exist in tropical Africa, Morocco, East Africa (Uganda, Tanganyika, Kenya, Sudan, Southern Rhodesia, etc.), but the absence of reliable statistics does not permit any definite conclusions to be drawn on the achievements in the drive against malaria in these lands. In tropical Africa malaria is transmitted throughout the year. The spread of malaria in the South-African Republic was formerly very extensive; the same was true of Madagascar. In these countries undeniable successes have been gained in combating malaria, but no precise statistical data are available.

On the American continent significant gains in suppressing malaria have been attained everywhere, but the greatest success in this field was achieved in the U.S.A. In the thirties of the present century malaria reaped rich harvests (up to 150,000 people) and caused great damage to the economy of the U.S.A. (up to 500 million dollars annually); however, by 1946, the number of cases had decreased to 48,610, by 1950 to 2,184, and in 1953, no more than 1,500 people suffered from malaria. At present malaria has practically been done away with in the U.S.A.

An intensive battle is waged against malaria in Brazil, where as many as 300,000 cases were registered in 1945, and in Argentina, where the number of cases attained 300,000 in 1951. Gains in the drive against malaria have been made in Panama, Guatemala, Honduras, Mexico, Ecuador, Nicaragua, Chile, and other American countries.

### FORMS OF MALARIA

As has already been stated, at present four species of malaria parasites of man are recognised; however, only three clinical forms of malaria correspond to these four species: 1) malaria tertiana (three-day malaria); 2) malaria quartana (four-day malaria); 3) malaria falciparum (or malaria tropica — malignant or tropical malaria).

*Tertian malaria* (caused by *P. vivax*) is observed both in temperate and in warm lands. This is predominantly a moderate form of the disease, the patients remaining ambulant; however, severe forms may also be encountered, particularly during pandemics, when the clinical course is similar to malignant malaria.

A variant of tertian malaria is caused by *P. ovale*, but it has now been firmly established that *P. ovale* is a distinct species,

The following proof of the specificity of *P. ovale* is particularly illustrative: its morphological aspects demonstrate certain traits likening it to the pathogen of quartan malaria, *P. malariae*, while its endogenous cycle of development is the same as in *P. vivax*; *P. ovale* evokes an alternation of paroxysms and afebrile periods analogous to those evoked by *P. vivax*; however, the form of malaria caused by *P. ovale*, follows a more benign course; besides, the paroxysms are observed predominantly in the evenings or at night.

*P. ovale* is rarely observed, and therefore it is of no great practical importance. The form of malaria caused by this parasite is found in Central Africa and, less frequently, in South America. Sporadic cases, mostly ecdemic, have been described in other countries and only a few cases in the U.S.S.R. (some authors doubt the presence of *P. ovale* in the U.S.S.R.).

*Quartan malaria (caused by P. malariae)* is less frequent than tertian and malignant malaria; it is observed in isolated foci the localities of which change with the passage of time.

The height of infection with quartan malaria occurs at the end of the summer and in the autumn; a typical trait of the disease is its tendency to relapses and prolonged courses (up to 3 years).

*Malignant (tropical) malaria (caused by P. falciparum)* is mostly found in hot countries, but is not restricted to them alone; it has been observed in the temperate belts as well. This form of malaria is characterised by a severer course than the previous forms, although its duration is usually shorter. The paroxysms usually appear in the later half of the summer, relapses occur in the summer and autumn months of the current year. Gametocytes appear in the blood next spring.

Aside from the principal species of plasmodia evoking different clinical forms of malaria variant immunological strains exist within the species themselves (*P. falciparum* and *P. vivax*).

It should be emphasised that these strains are characterised by differing degrees of malignancy.

In 1910 Grassi already differentiated two variants of *P. falciparum* in Italy; he called the first one "mitis", emphasising the milder clinical symptoms it provoked, and the second one "immitis", the cause of a heavier infection. It is also known that the Italian strain brings on a more severe course of the disease than does the Indian strain. *A. maculipennis* mosquitoes are easily infested with the Italian strain, but are resistant to the Indian; it has also been established that people who have recovered from the effects of infection with the Indian strain acquire no immunity against the Roman variety of *P. falciparum*.

Analogous data have been established on the Abyssinian (Ethiopian) strain of *P. falciparum*, the Panamanian, Mexican, and other strains.

The *P. vivax* species includes several strains differing chiefly by their incubation period and the clinical course of the disease they cause.

B. P. Nikolayev unites the so-called northern strains into a subspecies, *P. vivax hibernans*. The latter is localised in the temperate belt; the southern strains are common to latitudes south of 44° N, lat. A typical feature of

the malaria caused by the northern strain of *P.vivax* is the onset of the disease after a prolonged incubation period (from 6 to 14 months, but usually between 9 and 11 months). Infections caused by the southern subspecies of the parasite, *P.vivax* (B. P. Nikolayev), develop after a short incubation period (10-20 days). A protracted period of incubation (from 6-9 to 10-14 months, commonly 9-11 months) has been established for tertian malaria of the northern strain on the basis of observations conducted on a mass scale both in natural conditions and in experimental mosquito-bite infections (B. P. Nikolayev).

Following infection with the northern strain the first attacks of malaria are in the overwhelming majority of cases observed in April-August of the following year. Any widespread outbreak of acute febrile diseases in the north and in the temperate belt from April through June must be closely checked for malaria. In the southern regions infections caused by the southern strain of parasites are displayed in 10 to 20 days. In cases of malaria with protracted incubation periods the earliest relapses may often occur after an interval of 2-3 months. In the tropics (the southern Pacific) still another group of strains is observed (the Chesson strain, and others) that bring on paroxysms after a short period of incubation, with frequent early and recurrent relapses.

The geographic distribution of the different strains of malaria with long incubation periods is restricted in the U.S.S.R. to three zones (N. N. Dukhanina, 1957). The first zone, in the south, lies between 53° and 56° N. lat. The prevailing strain in this zone (up to 70 per cent of cases) is the northern one. In the second zone an even distribution of malaria with long and short incubation periods is observed. This zone includes the Ukraine, except for its southern regions situated south of 50° N. lat. in the east and 48° N. lat. in the west. The third zone is south of the second; it includes Moldavia, the southern regions of the Ukraine, the northern Caucasus, the lower reaches of the Volga, and the Black Sea coast. In this zone malaria with a long incubation period comprises no more than 20-30 per cent (in mountainous regions the percentage is higher). In the Transcaucasus and Central Asia this form is encountered in 10 per cent of cases (N. N. Dukhanina, 1957).

Malaria with a long incubation period is predominant in the Asiatic part of the U.S.S.R.—in Siberia. All three zones are present in Kazakhstan; malaria with a short incubation period is more frequent in the southern regions. This latter form of malaria is generally prevalent in the Uzbek, Tajik, and Turkmenian republics in Central Asia.

The usual incubation period for quartan malaria varies between 3 and 6 weeks, and for malignant (tropical) malaria it is 9-16 days (oscillations depend on the time of transmission of the infection, the severity of the epidemic, and the reactivity of the organism).

## CLINICAL ASPECTS

*Onset and development of disease.* Prodromal symptoms are usually insignificant in malaria: debility, malaise, headache.

Patients who have undergone several attacks of the disease and are in the latent interparoxysmal period may have a feeling of weakness and general indisposition, dryness in the mouth, pains in the joints and light chills the day before or several hours prior to an attack. Attacks of tertian and quartan malaria usually set in with shivering chills (ague). The fever rises to 38°C.

During the paroxysm the pulse is frequent, at times very full; sometimes vomiting may occur.

*Malignant malaria* is characterised from its very onset by muscular pains, splitting headache, general nervous symptoms, nausea, vomiting, and sometimes diarrhea. The initial chills are absent or very weak.

The febrile period may be of various duration, from several hours to 12-24 hours and more. At the height of the attack the general status of the patient deteriorates sharply: he is extremely restless, tosses around in bed, his face is flushed and his breathing is short. A very characteristic and frequently observed symptom pointing to involvement of the central nervous system is vomiting; it often leads to the erroneous diagnosis of an acute toxicosis, cholecystitis, gastritis, etc. In some cases acute gastrointestinal disturbance, urticaria, collapse-like states and cyanosis are observed. The temperature rises to 40-41°C. The tongue is swollen and covered with a white film. The skin becomes dry and red (in cases of protracted chronic malaria it stays pale during the paroxysm, acquiring a yellowish tinge). The pulse is frequent (100-110), soft, sometimes dicrotic. The upper level of the arterial pressure falls to 80-90 mm. The heart sounds are dulled, sometimes a blowing systolic murmur is heard at the apex and base. During the paroxysms a small quantity of concentrated urine is passed.

A frequent symptom of malaria is delirium, and occasionally convulsions and loss of consciousness (the latter for only a very short time).

Splenomegaly, hepatomegaly, and anemia comprise the well-known classic triad of malaria symptoms.

In malignant malaria splenomegaly appears later than in the tertian and quartan forms. The spleen is firm and tender to palpation.

Of no lesser importance in diagnosing malaria is the "liver symptom" — its enlargement and tenderness.

Malaria differs from the great majority of infections by still another important symptom — the development of anemia after a number of paroxysms.

Attacks of tertian and quartan malaria usually terminate in profuse sweating; sweating is not typical of malignant malaria; in the latter form it is either absent altogether or weakly expressed.

According to the old classic descriptions of malaria its paroxysms occur at certain times of the day: tertian malaria attacks continue for 6 to 10 hours on the average and are followed by a state of apyrexia; the sub-

sequent attack occurs on the third day (if the day of the preceding attack be considered as the first).

The pathogen of tertian malaria, *P. vivax*, goes through its endogenous cycle in 48 hours. Therefore, in typical cases the paroxysms are repeated on alternate days: the period of liberation of the merozoites into the hemoplasm from the ruptured erythrocytes coincides with the onset of the chills; the period of the ring form and half-grown schizonts corresponds to the high temperature; the subsequent stages of maturation of the trophozoites occur in the afebrile period.

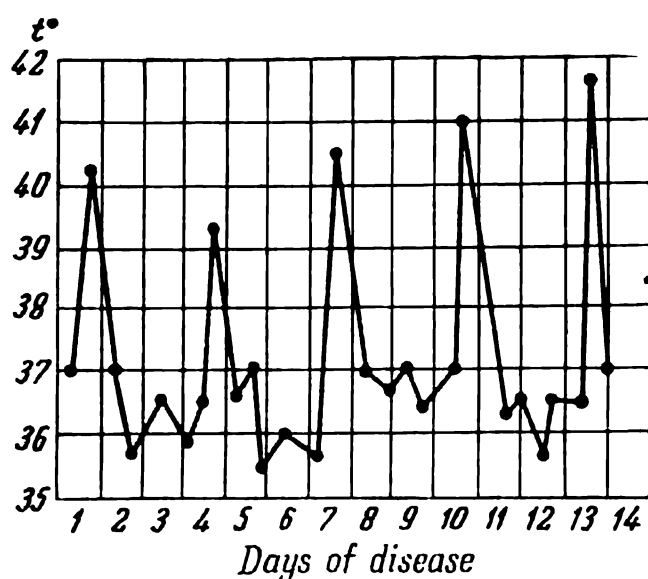


Fig. 6. Temperature in quartan malaria

Although there exists a close morphological resemblance between *P. ovale* and *P. malariae* the endogenous cycle of development of the former is the same as in *P. vivax*; consequently, the alternations of paroxysms and apyrexial states caused by *P. ovale* are the same as with *P. vivax*.

The paroxysms accompanying quartan malaria are more protracted. The endogenous cycle of development of the pathogen of quartan malaria, *P. malariae*, takes 72 hours, each attack being followed by two afebrile days (Fig. 6).

Malignant malaria is characterised by paroxysms occurring at irregular intervals, although frequently it is of the tertian type; however, in distinction from the latter the attacks are much longer, up to 24-36 hours, while the afebrile periods are shorter and are not clearly outlined (Fig. 7).

The total number of attacks (in the absence of treatment) reaches 10-12 and more. A particularly high number of attacks is noted in quartan malaria.

Fig. 8 shows a preparation of the blood of a patient afflicted with an algid type of malignant malaria and alimentary dystrophy; the hypoergic course of this case is illustrated in Fig. 9.

Modern clinical methods have introduced certain corrections into the outdated ideas on the acute course of malaria.

Even nineteenth-century authors quite frequently noted a daily type of fever in malaria, explained by them as being due to the independent con-

comitant development of two infections in the blood, contracted as a result of repeated mosquito bites on different days and hours. This gave rise to the term febris tertiana duplex, s.febris quotidiana; in febris tertiana anteponeus the intervals between attacks are shorter than 48 hours; in febris postponens this interval exceeds 48 hours, etc. (Fig. 10).

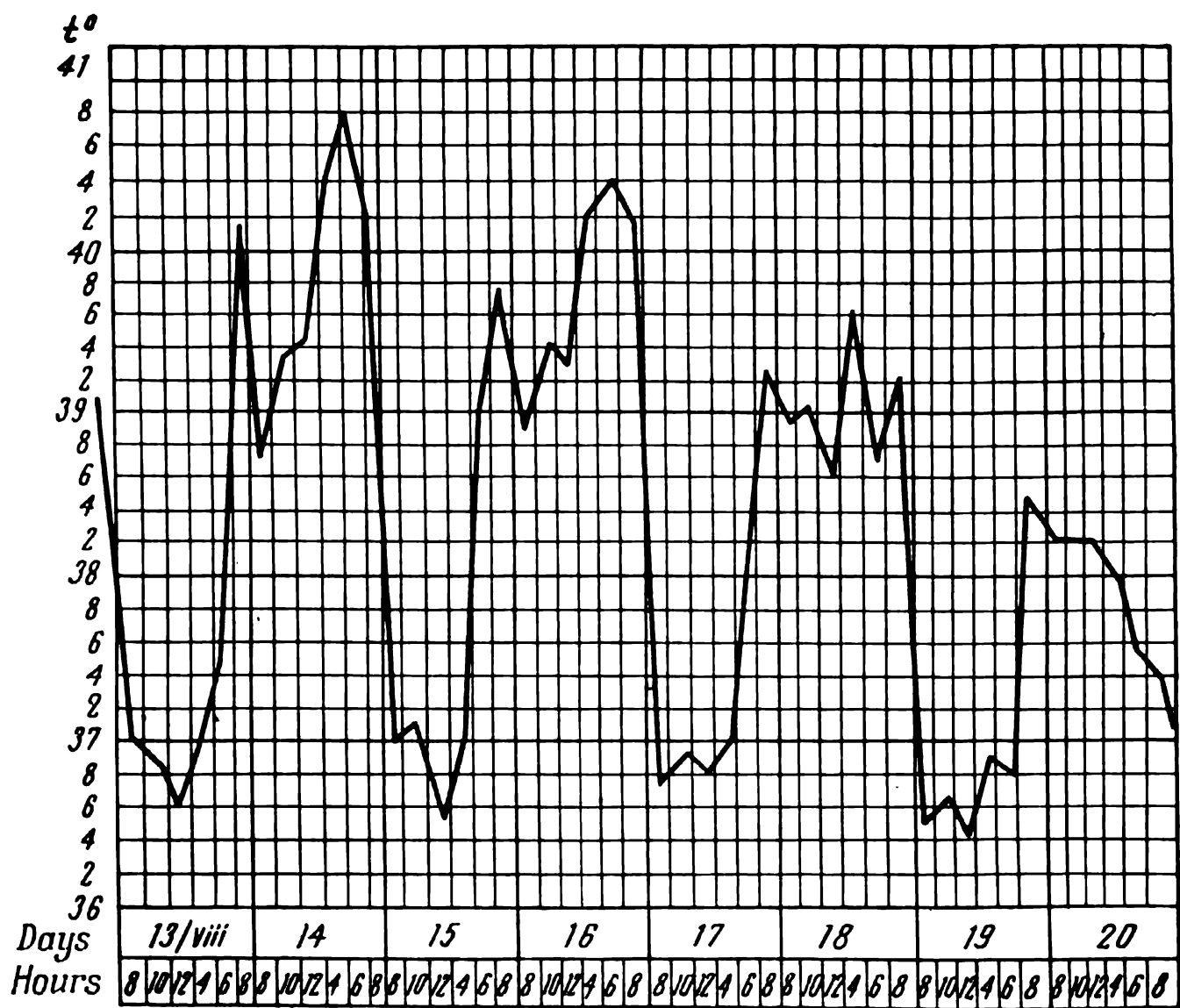


Fig. 7. Type of regular fever in malignant (falciparum) malaria

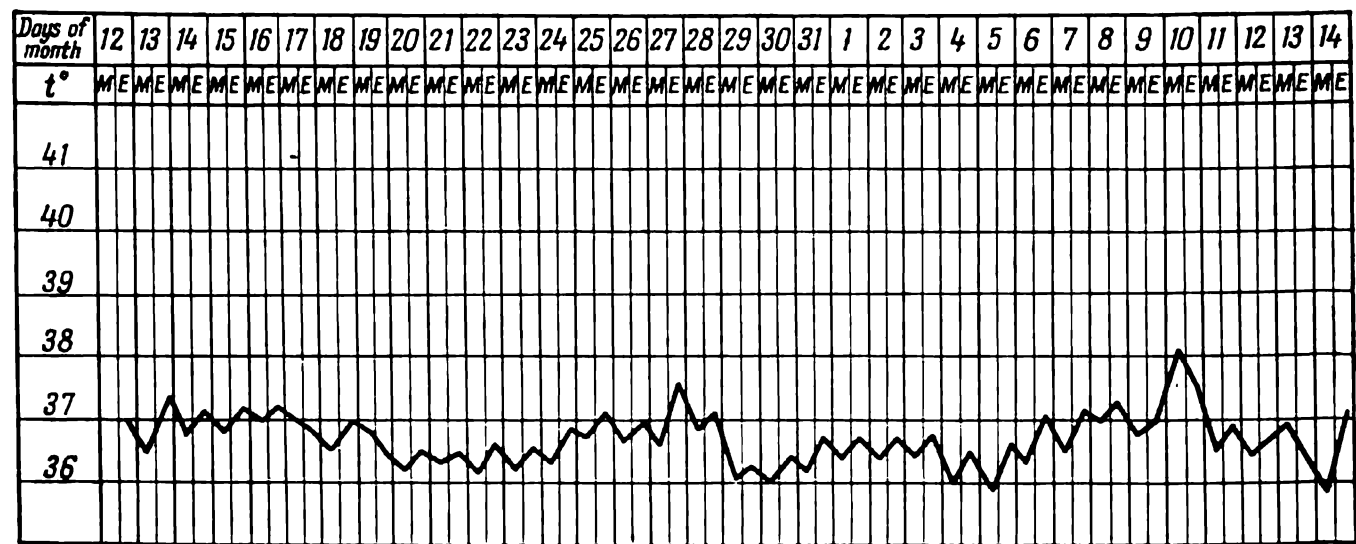
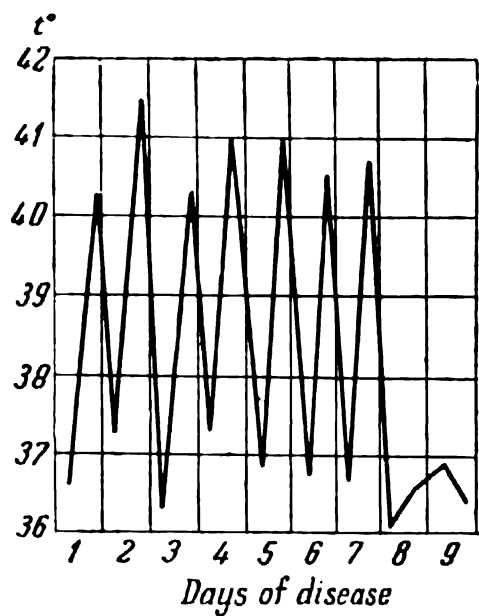


Fig. 9. Hypoergic course of tropical malaria in female patient with alimentary dystrophy

Without rejecting the possibility of double and triple infections with different species of malaria parasites that explain deviations from the typical temperature curve, it must, however, be emphasised that such

Fig. 10. Temperature in so-called malaria tertiana duplex



deviations are likewise observed in the course of single infections. Generally speaking, upon a closer study of malaria, particularly of the more severe cases, the frequency of irregular and subcontinuous fevers at the onset of the disease become clearly apparent (Fig. 11).

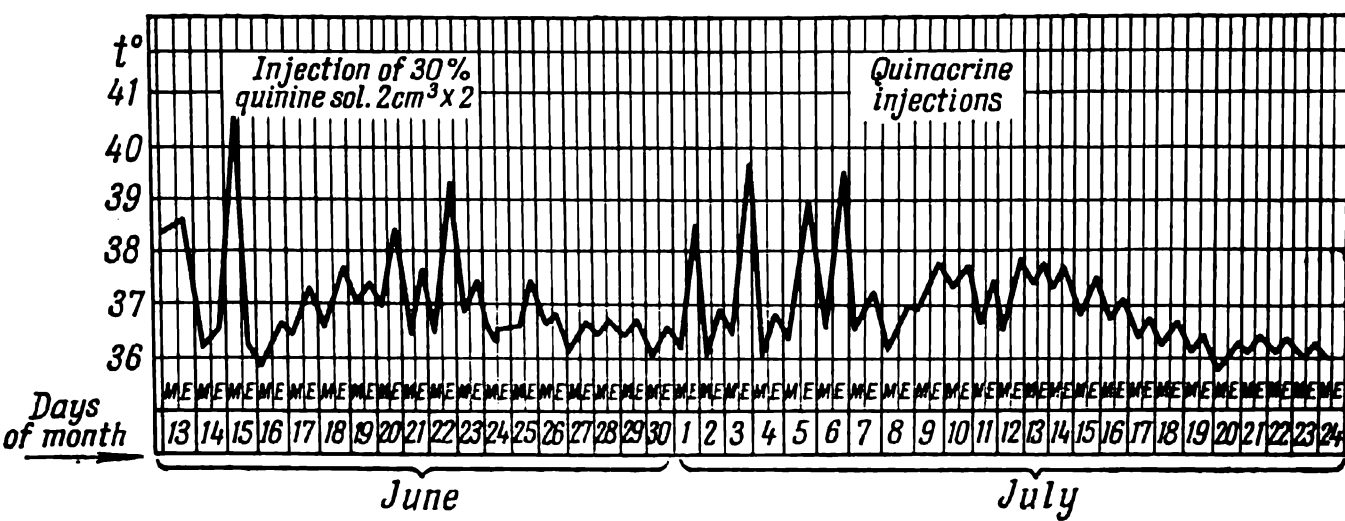


Fig. 11. Atypical temperature curve in malaria

These types of malaria are mostly observed in malarial sites or during pandemics. Most frequently three- to five-day monothermic or subcontinuous fevers (with remissions to 37.8-37.9°) are noted from the very first paroxysm; subsequently the paroxysms become more regular, during remissions the temperature falls to normal or subfebrile levels, but no regularity in the hours of the onset of attacks is observed.

A subcontinuous fever is characteristic of malignant malaria. Tertian malaria sometimes evokes a "paratyphoid" pattern: at the onset the evening temperature rising to 39° and subsiding to 37.8-38°C in the morning.



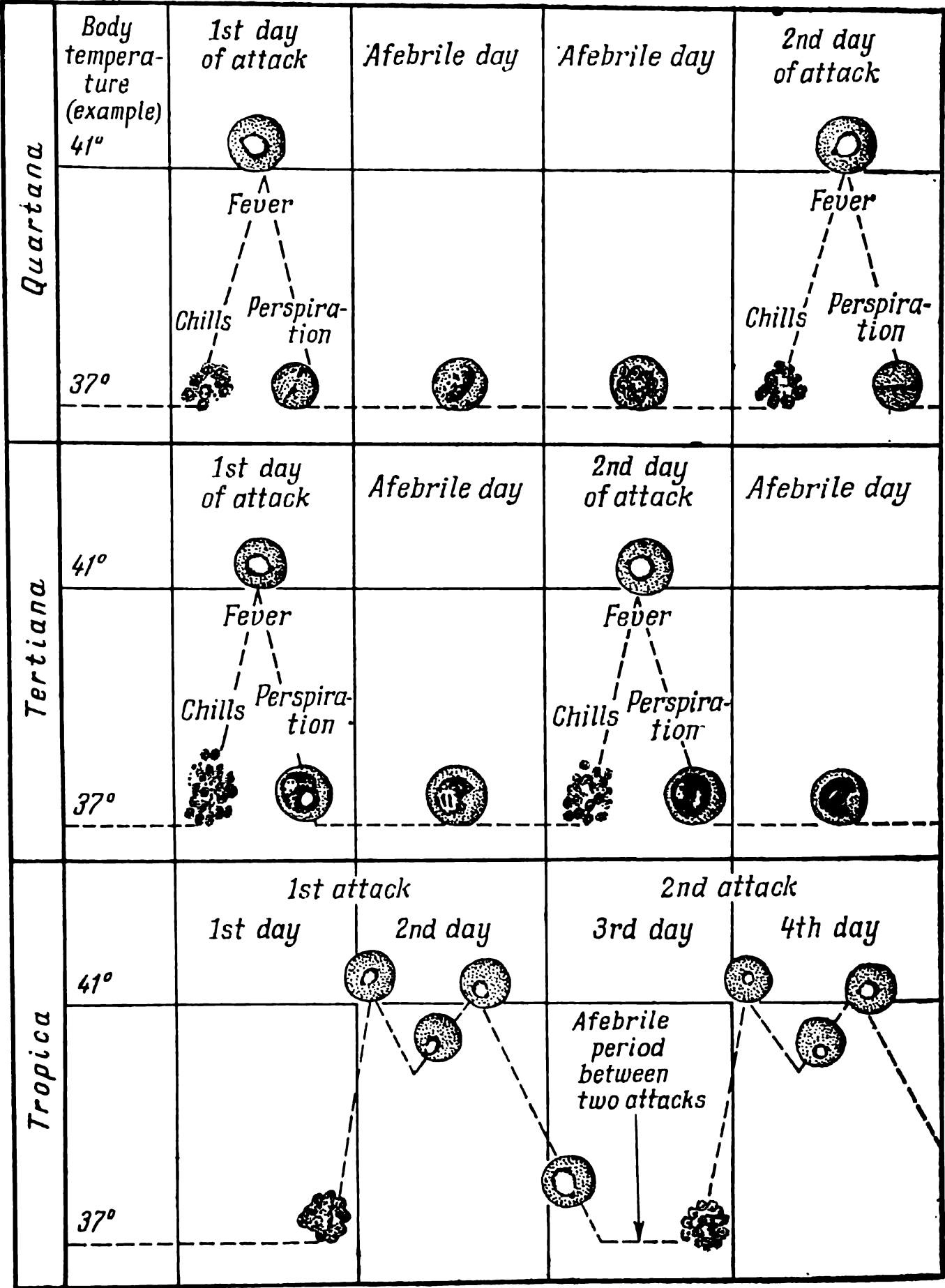


Fig. 12. Connection between fever and developmental stages of malaria parasites in human blood

All the classic manuals point out the close connections existing between the consecutive stages of malaria (chills, fever, sweating) and the different stages of schizogony (cycle of Golgi) (Fig. 12).

Such a schematic approach to the clinical aspect of the paroxysm and the dynamics of parasite development do not by far explain the diversity of the patterns of malaria infections. It is difficult to imagine that the relations between the two combatants — the microorganism and the macroorganism — can proceed along a rigid course. The Golgi scheme, necessary for teaching purposes, possesses a certain mechanistic element, while the explanation of daily paroxysms or typhoid-like courses of malaria as the result of double or triple infections is outdated and does not correspond to current views on the pathogenesis of the malaria infection, in so far as the onset of paroxysms and the occurrence of afebrile intervals are no “unilateral act dictated by the parasite” (S. D. Moshkovsky).

The peculiar periodicity of the attacks that distinguish malaria from other infectious diseases is determined by the behaviour of the microorganism, but the macroorganism introduces corrections into the Golgi cycle, or “law”, creating diverse clinical variations of the malarial process.

An important part in the course of the disease is played by the immunity developed in the human body, or, according to Sergent, premunition (see Immunity). If not for this immunity each and every malaria patient would without fail succumb to the gigantic invasion of his red blood cells.

It has been proved that the plasmodia are capable of evoking an attack of malaria if they number no less than 50 to 100 in 1 cu mm of blood, or 150-300 million in a person weighing 64 kg (Ross, 1902). If we are to assume that all the parasites were preserved, then one single tertiana parasite would in 12 days (in six merulation or trophozoic periods) generate 189 million plasmodia, and this amount is already capable of inducing a paroxysm. However, this is only a conditional figure, since the number of parasites in the entire body is much greater. In the most ordinary cases on the average two parasites are seen in one field of vision under the microscope (i. e., of 150 erythrocytes two are invaded). Let us assume that the body does not combat the infection, i. e., that it is completely devoid of immunity. In such a contingency the number of invaded erythrocytes would 48 hours later become 48 by 150, and in still another 48 hours (that is, after the second merulation) all the red blood cells in the body would be invaded by plasmodia. Practice has shown that death is inevitable when 25 to 40 erythrocytes per field of vision are invaded, and absolutely certain in total invasion of all the erythrocytes. The quantitative scale of invasion that would occur in unchecked multiplication of the plasmodia exceeds all imagination, its figures attaining astronomic values. Upon invasion of one-third of all the red blood cells the number of plasmodia would be 8,000,000,000,000. To count all these parasites at a rate of 100 per minute would take 130,000 years, and 550 years would be needed to examine them all under the microscope! And yet, theoretically, reproduction of the plasmodia in such gigantic amounts can occur within 4 to 6 days.

However, immediately upon the development of the malarial infection the organism mobilises and confronts it with such enormous numbers of immune bodies that, as a rule, 95 to 98 per cent of the merozoites perish without having had the opportunity of invading the erythrocytes.

The fierce battle waged by the organism against the plasmodia leads to a disturbance of the natural biological sequence in the development of the parasites: some of them perish, the development of others is retarded, and still others outstrip their mates. The result of this is a motley picture, including ring forms, semimature and mature schizonts. And at the same time there remains one leading generation that conditions the onset of the paroxysm; however, the small "companies" may, after several merulation periods, also turn into powerful generations capable of evoking paroxysms. And if we add to this individual neuroregulative processes the irregular occurrence of feverish attacks in malaria will become clear.

Protracted cases are characterised by paroxysmal temperature, the pattern may be very irregular and confusing: several attacks occur in a regular sequence corresponding to the given type of infection, and then the intervals between attacks become irregular (5-7-9 days).

The primary emergence of a fresh malaria infection with the above atypical beginning and typical feverish paroxysms (the so-called period of primary attacks) is usually replaced by a period of subsidence of the disease; the attacks cease for several weeks (sometimes even for 4-6 weeks), particularly if therapy has been vigorous. This period is followed by a period of *early relapses*. The total duration of the disease from its beginning to the end of the period of early relapses is two-and-a-half to three months.

After this comes the latent period of the infection, usually of one to one-and-a-half years duration. The latent period is the background for the so-called late relapses which resemble the primary paroxysms, but are shorter and milder. The distinguishing parasitologic feature of late relapses is that they usually appear in the presence of a large number of parasites in the blood. Every basic relapse is attended by a well-expressed or an attenuated early relapse 7 to 10 days after cessation of the fever; a new period of complete latency follows.

However, it is not always possible to place the course of a malaria infection into this strict cyclic framework that is, by the way, of great positive significance in working out practical medical measures for gaining mass control of malaria. Mild and moderately severe forms of malaria conform to the above scheme (the so-called ambulant type of malaria) in the central and northern belts of the Soviet Union.

In severe cases, during heavy outbreaks of the disease, or in hot climates even longer periods of active, persistent infections are observed; in these cases the acute period passes into a chronic state with protracted (over 4-6 months) active courses and marked visceral pathology. This type of malaria may be designated as a protracted, persistently relapsing form.

*Metamalarial period.* During this period a number of residual disturbances are observed (both functional and organic); they are the result of the malarial infection, but they have lost their etiologic specificity and are not connected with the activity of the plasmodia, as the latter are no longer present in the organism.

However, these residual disorders, inherent in pathological processes by the law of inertia, may progress and develop into severe pathologic conditions (metamalarial cirrhosis of the liver, metamalarial splenomegaly similar to Banti's syndrome).

#### CERTAIN ASPECTS OF THE PATHOGENESIS OF MALARIA

*Paroxysmal period.* The pathogenesis of the paroxysms of malaria is conditioned by the reproduction of the plasmodia. The onset of the attack coincides with the emergence of the merozoites into the plasma from the destroyed erythrocytes; although the enaction of the paroxysm is affected to a certain extent by the quantity of parasites present, still an overestimation of the importance of the quantitative factor in the pathogenesis of malaria leads to an incomplete understanding of the process. The paroxysms are caused by varying numbers of plasmodia in different people and at different periods of the disease; sometimes a very small number is sufficient (10-20 per 1 mm<sup>3</sup>) for the appearance of a severe attack (personal observations), and in other cases the attack does not occur in the presence of a great number of plasmodia.

At one time a so-called toxic theory of the malarial paroxysm was offered. According to this theory the paroxysm was brought on by an emergence into the blood of specific toxins formed upon the completion of merulation and destruction of erythrocytes (Mannaberg, 1899; Celli, 1913). Investigations undertaken for discovering these specific toxins were unsuccessful.

The majority of contemporary investigators take the following view of the origination of the paroxysm: the latter is formed as a reaction in response to protein substances appearing in the blood as a result of the death of the plasmodia in the merozoite stage. This opinion seems plausible, in so far as owing to premunition a great mass of the merozoites does not gain access to the erythrocytes and is destroyed. Y. M. Tareyev holds that an important factor in the formation of the malaria attack are the waste products formed by the disintegration of the erythrocytes and of the tissues in the body. And at the same time the clinic headed by Y. M. Tareyev has in recent years published a number of investigations in which the decisive role of neurological mechanisms in the appearance of the malarial attack is emphasised (V. I. Bobkova, 1952; N. N. Ozertsovskaya, 1955). These authors invest with particular significance the summation of excitation of the nerve elements in the central nervous system by the periodically reproduced parasites. Although we do not deny the participation of these mechanisms in the intensification or relaxation of the paroxysms, we do consider it necessary to stress that the *causative factors* inducing paroxysms are pyrogenic proteins, while the mechanism proper of the paroxysm is first of all associated, as in all pyretic reactions, with the effect of the pyrogens on the centre of thermoregulation.

There can likewise be no doubt of the importance of allergies in the realisation of the malarial attack and in the scope of pathologic mani-

festations of the disease; here allergy must be understood in the widest conception of the word, as it does not display the specific morphological traits of classical allergic diseases, such as rheumatic fever, for instance. The important role of allergic reactions in the pathogenesis of malaria is also confirmed by the fact that repeated attacks play the part of sensitising agents and lead to the development of severe clinical symptoms of malaria (coma, cerebral edema).

Malarial hemoglobinuria, hemorrhagic malaria, toxicoinfectious intestinal forms of malaria attended by characteristic crises (abdominal pains and urticarial rash all over the body) are very convincing proofs of an allergic pathogenesis.

Another thing to be remembered is that malaria is not restricted to hyperergic forms alone; it may manifest itself in *hypoergic and non-reactive forms*.

*Interparoxysmal (protracted) latent period and late relapses. Theory of James.* Up to now the question of the pathogenesis of the prolonged period of latency was solved quite simply: throughout the entire latent period of malaria a depressive cycle of schizogony occurs. This is evidently attended by the death of a great mass of the plasmodia in the merozoite stage, while the surviving parasites are so few that even though they do invade the erythrocytes they are incapable of provoking a paroxysm. This explains why no anemia develops during protracted latent periods, no hemolytic reactions are observed, and the discovery of plasmodia-invaded erythrocytes is extremely rare.

However, objections are at present raised against the theory of continuous schizogony. These objections are based on the following considerations: 1) no plasmodia are found in the blood in the period between relapses; 2) it is not clear why no protracted latent period or spring relapses are as a rule observed in cases of inoculated malaria (by schizont infection); 3) the human blood is not infectious in the days directly following infestation; 4) the administration of schizotropic preparations in the protracted latent period does not prevent the appearance of spring relapses.

A sporozoite theory was offered in 1937 by S.P. James for explaining the pathogenesis of the protracted latent period. The principle of this theory is the following: upon termination of the initial feverish syndrome the schizonts perish, but there remain histozoic or exoerythrocytic tissue forms that were developed from the sporozoites in the incubation period; these histozoites remain stabilised, and next spring they turn into the schizont forms that reproduce at a violent rate and call forth the relapses.

There is also a third, and very old, point of view that attempts to explain the pathogenesis of the protracted latent period and absence of parasites in the peripheral blood by the alleged penetration of the plasmodia into erythrocytes in the internal organs, where their development is somewhat retarded. For many years it was considered that the spleen, liver, bone marrow, and brain were the favourite sites of the plasmodia.

This conception is based on the allegedly prevalent discovery of plasmodia in the visceral organs while they are absent in the peripheral blood.

This "firm" establishment of the prevalent localisation of the plasmodia in the viscera is in contradiction with our investigations. The authors investigated 40 sternal puncture smears obtained from malaria patients and found that there were less parasites in the bone marrow than in the peripheral blood. F. M. Toporkov (1937) resorted to a clever procedure: at surgical operations performed on malaria subjects he obtained smears from the various organs — the bone marrow, ribs, spleen, epiphyses of the bones, the brain, the intestinal walls, etc. Circumstantial studies of preparations obtained from 282 patients convincingly proved that the plasmodia are found in the internal organs only when they are present in the peripheral blood, and are not discovered when they are absent from the peripheral blood.

Regrettably, many medical practitioners hold the erroneous opinion that in so-called insidious malaria the plasmodia repair to the visceral organs, and they consider it very desirable to do a sternal or splenic puncture in such cases for diagnostic purposes. Actually this investigation possesses no advantages and, moreover, its extensive application would not exclude the possibility of erroneous conclusions.

How does the parasitologic picture of the bone marrow differ from that of the peripheral blood? First of all, all the developmental stages of the gametocytes of *P. falciparum* are found in the bone marrow (small oval and spindle-shaped forms), and their number is much higher than in the peripheral blood (Z. M. Smolenskaya, 1946, 1948, 1954; T. K. Najmitdinov, 1940). It may look as if they simply accumulate in the bone marrow; however, taking into consideration the fact that they are demonstrable there in large numbers beginning with the eighth day of the initial onset of the disease and that all their stages are observed it must be concluded that their maturation occurs in the bone marrow (Fig. 13).

Moreover, according to L. F. Burova, G. A. Alexeyeva et al., all the stages in the evolution of *P. falciparum* are demonstrable in the bone marrow and spleen—from the ring form to the mature schizont (with the exception of very heavy infections with malignant malaria when all the phases of division of *P. falciparum* are observed in the peripheral blood).

However, Z. M. Smolenskaya, having investigated 150 patients with malignant malaria (in Samarkand) both during paroxysms and afebrile interludes, does not agree with this statement. By comparing the age contingents of *P. falciparum* in sections of the circulatory system accessible for life-time parasitologic examinations (bone marrow, spleen, venous blood, peripheral blood from a finger) for the purpose of clarifying the localisation of the schizogony of the pathogen of malignant malaria, she established the following:

1. During all the phases of the malarial process attendant on an ordinary course of the disease only young ring forms are found in smears obtained by sternal punctures and in the peripheral blood extracted from a finger, while the divisional forms are entirely absent.

2. Studies of smears made with simultaneously extracted spleen and peripheral blood specimens (by splenic puncture and from the fingers)

in cases of malignant malaria during various phases of the disease in its ordinary form demonstrated the absence of any dividing forms.

3. Upon examination of the venous blood of the upper and lower extremities in ordinary cases of malaria it was found that in 7 per cent of cases this blood contained, besides the ring forms of the pathogen of malignant malaria, also stages of division absent in the blood extracted from the fingers.

4. Post-mortem examinations showed the presence of small accumulations of the parasites in the venules of the adipose tissue, these accumulations containing generations of all ages; from fine, pigmentless schizonts and schizonts ripe for division to schizonts broken up into merozoites.

The discovery of divisional phases of *P. falciparum* during autopsies only in the venules in their absence in the other sections of the circulatory system explains the presence of divisional forms of this parasite in the venous blood.

### PLASMODIA CARRIERS

Parasite carriers are individuals in whose peripheral blood the parasites are demonstrable in the absence of any clear clinical symptoms characteristic of malaria. Parasite carriers may reveal the various phases of the malarial infection. Sometimes such individuals are people who never displayed nor display any clinical symptoms of malaria at all.

Carriers are important epidemiologic factors, since for such persons, being practically healthy, do not apply for medical aid, while they are actually concealed sources of the infection.

The condition may be observed in persons who have recovered from malaria, or in recent convalescents—from 2-6 weeks to 6-12 months after paroxysms; in the first case the time coincides with the earliest relapses, in the second—with the late relapses. The parasite carrier does not always exhibit complete absence of all symptoms. A thorough medical investigation of such persons usually reveals brief periods of fever, indisposition, anemia, etc. Parasite carriers may conditionally be divided into two groups of persons in whom the plasmodia are discovered at the time of the examination and who either were formerly afflicted with malaria but manifested no clinical symptoms of the disease lately and within two weeks after the examination, or persons who never suffered any acute attacks of the disease. During the last war the specific gravity of parasite carriers in the overall quantity of malaria sources was high, sometimes reaching 30 to 40 per cent.

Carriers are an important epidemiologic feature in malignant (*falciparum*) malaria. In people who have contracted the disease in the third quarter of the year the acute symptoms usually subside by next spring and the majority of these patients may be considered to have recovered. Only a small part of such individuals are found to be parasite carriers during the spring and summer following the year the infection was contracted, and mainly gametocytes are demonstrated in their blood. This may cause mass infestation of the mosquitoes of the first generation of the year.



The absence of parasite carriers would make the propagation of malignant malaria impossible in the year following an outbreak. Consequently, the discovery of carriers of *P. falciparum* and their treatment are an extremely important prophylactic measure (P. G. Sergiyev and A. I. Yakusheva, 1956).

A certain part in the general source of infection with tertian malaria is played by plasmodia-carriers.

Children are often carriers of the infection, manifesting massive reproduction of the plasmodia and the appearance of a small number of gametocytes. The child carriers undergo no typical attacks of the disease and have no fever.

### CLASSIFICATION OF MALARIA

On a general scale malaria (mild and moderately severe cases) fits into a periodic systematisation as a polycyclic disease (*period of acute paroxysms — early relapses — interparoxysmal period — late relapses*); this classification was evolved in the Central Institute of Malaria in the Soviet Union.

Malaria is a disease that affects the population on a mass scale, therefore the above simple scheme is highly important in practice and invaluable in the enaction of the regular systematic treatment and prophylaxis of malaria.

However, malaria sometimes displays a diversity of clinical symptoms and the attending doctor must decide what phase of the disease and what organic and systematic pathology he has to deal with. Correct and universal therapeutic tactics can be evolved only following the solution of this problem.

The authors' observations of heavy malarial infections in the hot belt of the U.S.S.R., and also in malaria-ridden sites in the central belt of the Russian Federation (R. S. F. S. R.) have enabled them to identify as a discrete group malaria infections with undeniably *protracted courses* (*persistently relapsing forms*), or a protracted form associated with constant re-infection, when the malarial process proceeds for months and is characterised either by clear-cut pyrexial and visceral symptoms, or by protracted afebrile periods with quite definite visceral and nervous pathology.

Finally, the authors have put the so-called *metamalarial* (postmalarial) forms of the disease under a separate heading. These forms are associated with plasmodial invasion which occurred in the past, and the disease manifests its full force at a time when there are no longer any plasmodia in the patient's body, or when they have already become almost inactive: the subsequent development of the pathologic process that began at the time of plasmodial invasion greatly outstrips the boundaries of the specific form of malaria.

The malarial disease itself, connected as it is with the active development and metabolism of the plasmodia, calls for energetic specific treatment under the effects of which it is subject to reverse development; specific antiplasmodial treatment is of no avail in the metamalarial form of the disease.

Below we present a classification of the different forms of malaria.



### Group a

I. *Fresh (recent) malaria infections* (malaria recens): congenital malaria, primary (initial) malaria, re-infection, inoculated malaria (acute paroxysms).

II. *Early relapses.*

III. *Interparoxysmal periods*: 1. short (between the closest relapses); 2. winter latent period.

IV. *Protracted malaria*:

a) a form associated with frequent paroxysms of high temperature and pronounced visceral pathology;

b) the visceral form, accompanied by no clear temperature relapses (only rudiments, subpyrexial forms);

c) latent malaria accompanied by indefinite visceral and neurological symptoms (this form includes so-called masked malaria).

V. *Late relapses.*

### Group b

#### *Metamalarial diseases*

### FRESH (RECENT) MALARIA INFECTION

*Congenital malaria.* Congenital malaria possesses some specific features; it frequently acquires an atypical pattern.

The mechanism effecting the appearance of congenital malaria is mostly associated with intrauterine (transplacental) infection, but the infection may be contracted during parturition if it gains access to the fetus via the severed umbilical cord from the mother's blood (for instance, upon rupture of the perineum). In the latter case the child is usually born healthy and develops the disease after an incubation interval of 10 to 14 days.

Many cases have currently been described in which malaria was discovered in the newborn directly after delivery, or on the next day. Congenital malaria is quite widespread in warm lands where its treatment is not adequately managed.

The clinical symptoms of congenital malaria are characterised by a number of specific features. Frequently the babies are delivered prematurely, with enlarged spleens. Plasmodia are often demonstrable in their blood in the absence of clinical symptoms. Underdevelopment, anemia, and jaundice are marked. Sometimes the disease is not attended by elevation of temperature; paroxysms in the newborn may be accompanied by convulsions. The feverish forms may continue for 5-6 days.

*Initial malaria.* Initial or primary malaria manifested after a short or long incubation period calls for no special explanation, but it is highly important to distinguish relapses from re-infections.

Upon attending a patient who has had malaria 3 or 4 years previously and who at the time of examination manifests renewed attacks of a severe and persistent nature with very protracted active periods, some doctors do not hesitate to diagnose them as relapses of the primary malaria from which the patient had recovered 3-4 years ago. However, relapses after such a long time are exceptions, and not the rule, and besides, relapses occurring after such a long period (if they are possible) are by no means capable of

evoking such protracted, persistent and severe courses. This is a re-infection.

**Re-infection.** Re-infections are natural to malaria, a disease that is known to produce no stable immunity after initial infection (particularly to another species or strain of the parasite). Re-infection is understood as a repetition incursion of malaria that appears after two or more years since the last attack. The past history of the case is also a means of distinguishing re-infection from an initial infection. The course of repeated malaria due to one and the same species and strain of the parasite is usually milder than the initial disease, owing to a certain immunity developed after the first bout with the disease; but if the pathogen belongs to various strains (northern and southern), or a person who has had tertian malaria is re-infected with malignant malaria the course of the re-infection may be even more severe than that of the first infection.

**Inoculated malaria.** There exist two forms of malaria inoculations (depending on the method of inoculation): *schizont inoculation*, when the blood of a malaria patient is introduced into the recipient, and *sporozoite inoculation*, obtained as a result of experimental infection of the recipient through the bite of an infested mosquito. The course of the first form is very mild and it responds to treatment easily. The course of the second (sporozoite) form is analogous to natural malaria.

**Recent (fresh) malaria** commonly takes an ordinary course (see Forms of Malaria); however, in certain cases, particularly in the southern areas, recent malaria may run an atypical course. We distinguish a number of pernicious forms of recent malaria, among them typhoid-like, icteric, tox infective, hemorrhagic, comatose (cerebral in the wide sense), psychotic, hemoglobinuric and other forms.

The chapters *Early relapses* and *Interparoxysmal period* (latent period) have already been dealt with.

**Protracted malaria** (*malaria protracta, prolongata*). We insist on classifying this form separately as it is observed quite frequently, particularly in unhealthy malaria-ridden sites in hot and tropical climates, where the malarial process takes a very persistent course.

Our clinical observations have been completely confirmed by the observations of malariologists in Azerbaijan, Armenia, Moldavia, Rumania, and in other countries.

It has at present been established that tertian malaria forms recurring persistently over periods of 7-9 months, are caused by a particular strain of the *Plasmodia*, the Chesson strain, described as native to south-eastern Asia.

Certain authors who are not sufficiently conversant with the clinical aspect of malaria in warm climates are against placing protracted malaria under a special heading. Having had no opportunity for studying such forms, having observed malaria solely in the central belt of the U.S.S.R., and even then only medically treated cases, these authors make a one-sided, dogmatic approach to the clinical course of malaria. And what is more, they fear that the term "protracted malaria" may lead to the mis-

taken concept of malaria being an essentially chronic disease. We cannot agree with this point of view. We ourselves object to the term “chronic malaria”, as medical practitioners endow it with an erroneous conception of malaria as a typical chronic disease similar to tuberculosis, syphilis, etc. Malaria is a cyclic (polycyclic) disease that commonly terminates in periods under two years. But as regards the persistently recurrent forms of this infection, presenting a series of periodic pyrexial peaks and visceral symptoms over a period of 5-6 months, the usual scheme (acute paroxysms — interparoxysmal period — late relapses) is not applicable.\*

It is namely the diagnosis “protracted malaria” at a period when the visceral pathology is directly associated with the intensive activity of the plasmodia that will unfailingly lead to a delineation of the required course of therapy, to a proper method of treatment of the visceral symptoms.

There is still another argument in favour of placing “protracted malaria” under a separate heading. It must be noted that the opponents of the assignment of a special place in the classification table to this form of the disease associate their concepts with the clinical symptoms of treated malaria. However, an actual and full clinical conception should be based on the study of spontaneous courses of the disease. The following analogy is quite illustrative in this connection: after the introduction of contemporary methods of treatment of syphilis and tuberculosis many doctors have been known to declare that these diseases have long acquired a new course and that their old clinical pattern has faded into the past.

It is only natural that just as the clinical descriptions of syphilis and tuberculosis cannot be based on observation of treated cases so it is wrong to deny at present certain forms of malaria that would, if left to themselves, display their true pathologic nature.

Finally, one more comment. In warm lands a variety of protracted malaria is often observed, when the patient is recurrently, over a period of several seasons, subjected to *re-infection*. Re-infection is particularly frequent in children. The clinical symptoms are the same as for a primary case of persistently recurring malaria.

*Protracted malaria shows three basic varieties:*

- a) *a frank form*, running a course with frequent paroxysms of fever and more or less pronounced visceral and neurological symptoms;
- b) *a frank form in which visceral symptoms prevail, without clear relapses of fever* (paroxysmal rudiments, rarely true paroxysms);
- c) *a latent form* unattended by relapses of fever (subpyrexial) with mild visceral and neurological symptoms (this also includes the so-called masked malaria).

With diagnostic and therapeutic aims in mind we recommend form specification in diagnosing malaria, with indication of the organs or systems most pronouncedly involved, for instance: *protracted malaria (ictero-anemic form)*; *protracted malaria (splenomegalic form)*; *protracted malaria*

---

\* The authors have observed patients of this type during heavy outbursts of the disease in localities where re-infection was impossible (!).

(*neuro-psychotic form*), etc. Emphasis on these details will facilitate the planning of a clear and purposeful therapeutic course.

*Concealed (latent) malaria.* A subdivision under the heading “protracted malaria” must be allotted to concealed or latent malaria (*malaria latens*). This form is also a protracted process; however, contrary to the above-mentioned frank forms of protracted malaria it is only manifested by rudimentary symptoms that correspond, however, to the clinical symptoms of malaria. Latent malaria does not signify interparoxysmal latency. The form “latent malaria” implies a protracted, active form of malaria that has “hidden” itself and only displays mild, partly obliterated, symptoms. The interparoxysmal period is a prolonged interlude of comparative well-being; latent malaria is a morbid, subcompensated state.

Naturally, in this case we must remember the *secondary latent malaria* that appears after the acute period of initial attacks.

*Primary latent forms of malaria*, i.e., forms of a concealed nature from the very beginning, with no plasmodia found in the patient’s blood, deserve a critical consideration.

It seems most likely to the authors that a thorough study of the past history of cases of this type would reveal several paroxysms of fever, much weaker ones than in typical malaria.

Forms of malaria with prolonged incubation periods likewise cannot be looked upon as primary malarial latency, as in these forms no symptoms of the latter have been confirmed throughout the protracted incubation period (observations of artificial infection of human beings with the northern strain of *P. vivax*).

Masked malaria (the *malaria larvata* of the old authors) we positively include in the latent form, and do not place it under any separate heading.

As may be seen from the term itself (larva—guise, mask) *malaria larvata* implies such forms of malaria when the disease attires itself in the guise of other diseases that have no resemblance—or only a very slight one—to malaria. This, for instance, includes the intermittent pains in the area of the liver that are taken for attacks of cholecystitis, but are actually associated with the development of hepatitis, and disappear under specific treatment for malaria; the intermittent arthralgic pains, neuralgia (e.g., pain in the trigeminal nerve), afebrile urticaria, etc.

However, although we do agree with the existence of latent (and of masked) malaria, we should like to point out that this diagnosis should be very guarded, all the more so as latent malaria is extremely rare. In cases of clearly obvious clinical findings emphasised by a number of definite symptoms there is no need to resort to this diagnosis, as a diagnosis of protracted malaria will be more correct.

However, while recognising latent malaria as a form of the disease it is dangerous and unnecessary to “label” many patients with this diagnosis. We advise great caution to be exerted in this matter and warn of the danger of falling under the influence of the layman, of patients who may have

been so affected by the severity of their former attacks that, not really knowing the truth about malaria, they are prone to find "latent malaria" in themselves almost throughout their entire life.

The diagnosis of "latent malaria" is confirmed by a marked therapeutic effect resulting from the use of quinacrine, bigumal, quinine and other antimalaria preparations.

"Latent malaria" is also confirmed by the discovery of plasmodia throughout a prolonged period of observation of the patient.

Another pitfall to be looked out for is the possibility of diagnosing a prolonged subfebrile condition as being of malarial origin.

Prolonged subfebrile conditions are by no means characteristic of malaria, and if it be observed in malaria convalescents it is the result of postmalarial changes in the autonomic nervous system and its centres (so-called non-specific postinfectional subfebrility) and by no means the result of metabolic activity of the plasmodia.

In conclusion we wish to point out that the latent period may be replaced by a transition to active malaria with characteristic relapses.

Late or remote relapses appear after latent periods exceeding 3-4 months; in various forms of malaria (most commonly in tertian malaria with a short incubation period) these relapses appear in the spring (in the central belt of the U.S.S.R. at the beginning of April, down south—in March); malignant malaria is, moreover, characterised by the appearance of isolated relapses in the late autumn.

*The group of metamalarial disorders* includes conditions wherein the significance of the parasite is reduced to merely its "historic" role in the evocation of the disease, but the pathological process has already outstepped the framework of the specific malarial form. Here there is no longer any malaria per se. This condition is already the sequel, the "afterword" that has in itself become a cause (Y. M. Tareyev).

The group of postmalarial conditions should include metamalarial hypogenerative anemia, polycirrhosis (hepatolienal syndrome), etc. In such cases the specific antimalarial treatment administered successfully for conditions enumerated in group A are of no avail. The time of the invasion with the plasmodia is sufficiently remote (the parasites are not demonstrable in repeatedly extracted blood specimens). Proceeding from this position we consider it apposite to employ the term "metamalarial" (meaning "postmalarial") pathologic conditions, instead of the term „paramalarial" (meaning "concomitant with malaria").

In supplement to the *classification* we recommend that a parasitologic characteristic of the disease be made.

We shall now turn to the clinical features of malaria.

Many years ago G. A. Zakharyin stated that diagnosis should embrace the "principal disease", secondary disorders, and all the individual aspects of the case. Therefore segregation of comatose, typhoid-like and other forms of the disease, as well as the nature of the localised clinical symptoms in protracted cases and in metamalaria, etc., are the best means for characterising the clinical features of the ailment.

Thus, in the final analysis the grouping of malarial afflictions we have proposed should be supplemented by parasitologic and localisation characteristics. For instance:

Malaria tertiana primaria protracta cum anaemia et splenomegalia (schizonts + *P. vivax* gametocytes).

Malaria tertiana protracta. Hepatitis malarica (schizonts + *P. vivax* gametocytes).

Malaria tropica (falciparum) recens (early relapses).

Coma malaricum (schizonts + *P. falciparum* gametocytes).

Metamalaria – cirrhosis hepatis metamalarica.

### PERNICIOUS FORMS OF MALARIA

In warm (particularly tropical) climates, and also in heavily infested malarial areas pernicious forms of malaria are frequently encountered. Some authors hold them to be special forms of the disease. The pernicious forms are all characterised by severe clinical courses, frequent transition to comatose malaria, and sometimes poor prognosis (particularly in neglected cases).

#### The typhoid-like form

This designation implies forms of malaria characterised by protracted fever (8-10 days) of a monothermic or subcontinuous type (Fig. 14). The patients present a typhoid-like status.

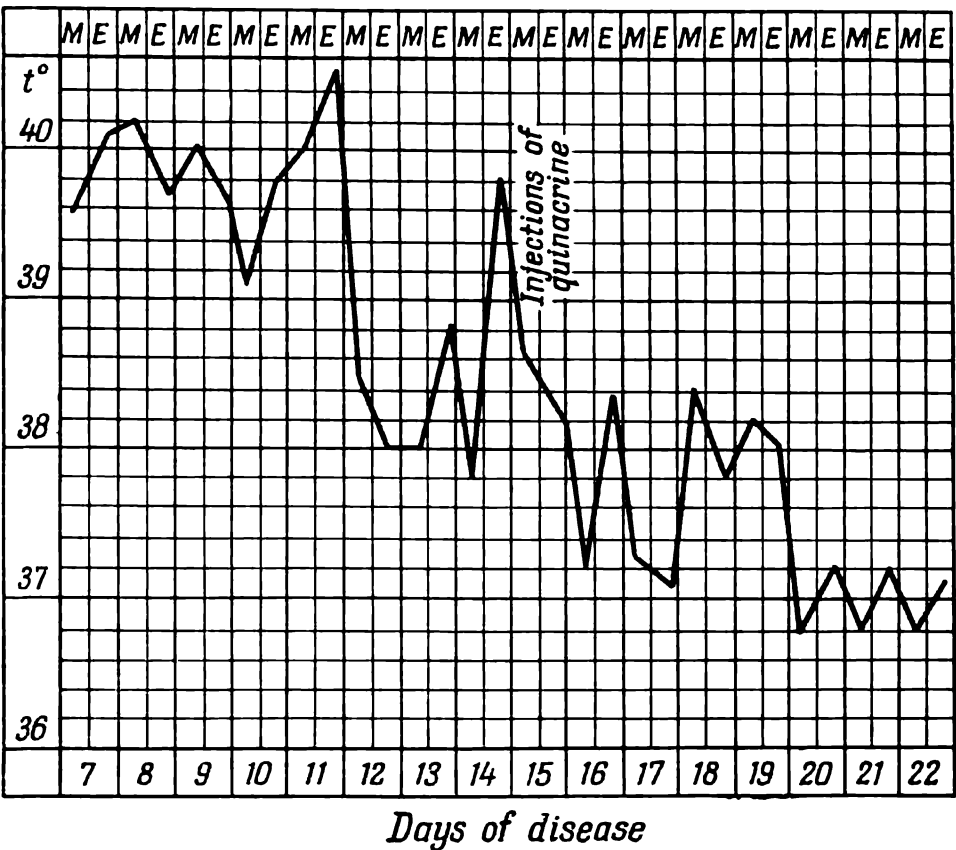


Fig. 14. Tropical malaria developing with a typhoid type of fever

Naturally, one should be able to differentiate these threatening forms from true typhoid, but in certain cases this is almost impossible to do on a purely clinical basis. Malaria is indicated by a more violent course of the disease: early psychotic disturbances, marked tachycardia, acute sensitivity of the liver, early enlargement of the spleen. The decisive factor is the demonstration of plasmodia.

It is mostly malignant tertian malaria that acquires the typhoid-like forms, but the authors have also had occasion to observe a typhoid-like course at the onset of the disease in cases of benign tertian malaria.

### **The bilious form**

The bilious component is one of the general features of malaria in so far as the malaria parasite destroys the erythrocytes thus leading to the development of hemolytic jaundice. However, the intensity of this jaundice is not great, and it develops gradually, as the morbid process intensifies.

We understand the icteric (or bilious) form of malaria to be such a form of the disease when the bilious symptom, owing to its intensity, comes to the foreground of the clinical picture, and the bilirubin content in the serum is noticeably elevated.

Bilious malaria is observed in two variants, the hemolytic and hepatic forms. In the first instance sharply increased disintegration of the red blood cells is present, explicable not only by the hemophagic function of the plasmodia, but also by the increased blood-destructive activity of the reticuloendothelial system (intracellular hemolysis).

In acute cases of malaria the patients sometimes become bilious and anemic quite soon. Such forms are frequently pernicious. The patients show signs of hemorrhagic diathesis. In most cases these forms are combined with a typhoid-like feverishness, or a comatose condition.

In Central Asia acute, severe icterohemolytic forms of malaria were formerly observed in definite localities. For instance, Tarmez, Merv, Kushka were once notorious for an abundance of bilious forms of malaria. As regards malaria jaundice connected with liver retention it must be stated that its direct association with malaria is doubtful. There are grounds for presuming that this condition may be due to the superimposition of the Botkin disease (epidemic jaundice).

### **Malaria hemoglobinuria**

Synonyms: malarial hemoglobinuria, hemoglobinuric fever, quino-malarial hemoglobinuria (Russ.); febris biliosa haemoglobinurica (Lat.); Schwarzwasserfieber (Germ.); hemoglobinuric fever, blackwater fever, redwater fever, canebrake yellow fever (Eng.); fièvre bilieuse hématurique (Fr.).

*Definition.* In the narrow classical sense this is an acute paramalarial condition appearing predominantly after the ingestion of quinine; it is



characterised by violent and multitudinous disintegration of the erythrocytes and the development of hemolytic jaundice and hemoglobinuria; in the wider sense it is a condition characterised by acute multitudinous intravascular hemolysis under the influence of various medical preparations and other causes (cold, long marches, poisoning, etc.). The complex of symptoms of hemoglobinuric fever has long been observed and described, but it has often been confused with bilious typhoid and yellow fever. The scientific description of malarial hemoglobinuria as a paramalarial disease was published by the French physician Lebeau (Madagascar, 1850). In the United States hemoglobinuric fever associated with malaria was described by Cummings (1859) in Louisiana.

The first fundamental works on malaria in Russia were the reports published by a prominent pathologist of his time, V. I. Afanasyev (1881, 1885); this author demonstrated the frequent association of hemoglobinuric fever with malaria in the presence of an auxiliary chemical agent (such as diamine toluene). A. D. Grekov and M. Konstantinov (Central Asia, 1900-1901) compiled one of the most comprehensive statistics of those days for hemoglobinuric fever caused by malaria: 40 such cases were revealed among the 21,300 malaria patients registered in the Merv region. During four subsequent years of work in this region A. D. Grekov described 200 cases of hemoglobinuric fever. In all a total of 337 cases of malarial hemoglobinuria were described in the period previous to and including the 1930's (P. P. Popov). The idea of an association between blackwater fever and quinine was first conceived by the Greek physician Veretas.

This thought was supported by Tomaselli and Koch. The general incidence of hemoglobinuric fever is rare, its annual rate even in countries widely subject to malaria does not exceed several hundred cases. In the Soviet Union only sporadic cases have been observed of late.

Hemoglobinuric fever is observed among all peoples in all three forms of malaria, but it is predominant in malignant tertian malaria (Fig. 15). The highest incidence is registered in Africa, mostly in West Africa. The incidence is particularly high in the deltas of the Niger and Gambia rivers, and also on the banks of the Senegal and Kwansa. In East Africa blackwater fever is observed in Mozambique, the valleys of the Shire and Zambesi rivers, in Tanganyika, Uganda, North and South Rhodesia, Ethiopia, and the valley of the Nile; in North Africa—in Algeria, and also in certain areas of Madagascar.

In Asia many cases of hemoglobinuric fever have been registered in the valley of the Jordan, in Afghanistan (personal communication made by G. A. Alexeyev, 1957), in India, on Ceylon, in Burma, in the vicinities of Tonkin, in the Malayan Federation, North Thailand, China (Yunnan, Taiwan), Java, the Solomon Islands, New Guinea. On the American continents: North America—in the U. S. A. (Florida, Alabama, Mississippi, Arkansas, Texas, North Carolina and Virginia); in Mexico; in Central America—in Panama, Guatemala, and other areas; in South America—in Venezuela, and also in the West Indies. The condition has been observed



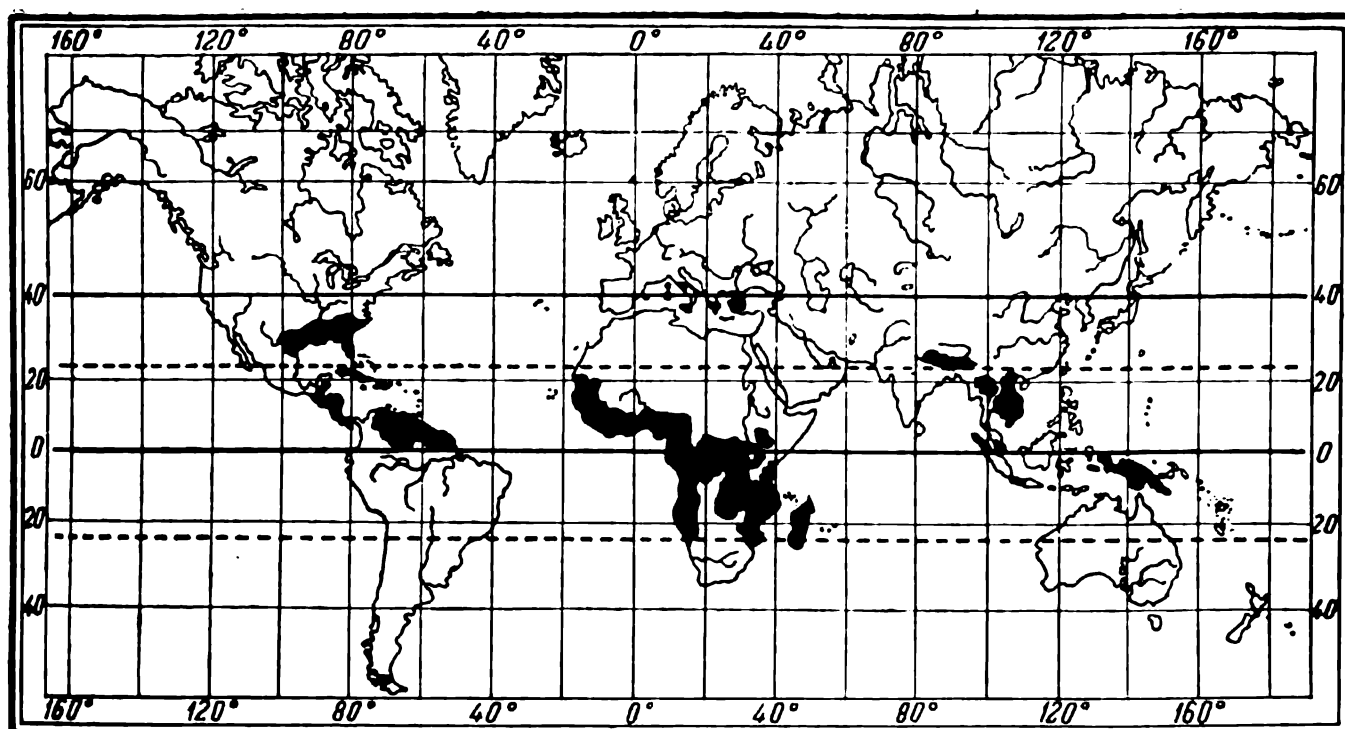


Fig. 15. Geographical distribution of blackwater fever (malarial hemoglobinuria) (Stitt)

in Europe — in Bulgaria, Yugoslavia (Macedonia), Albania, Greece, Italy (Sicily, Sardinia, and Central Italy).

The *etiology* and *pathogenesis* of this condition are closely interrelated. Classical malarial hemoglobinuria (blackwater fever) is observed only in malaria patients, predominantly in the active phase of this disease, but it has been noted in the latent form as well. Various theories for the explanation of malarial hemoglobinuria were offered in the past, descriptions were made of independent pathogens of this disease — piroplasma,

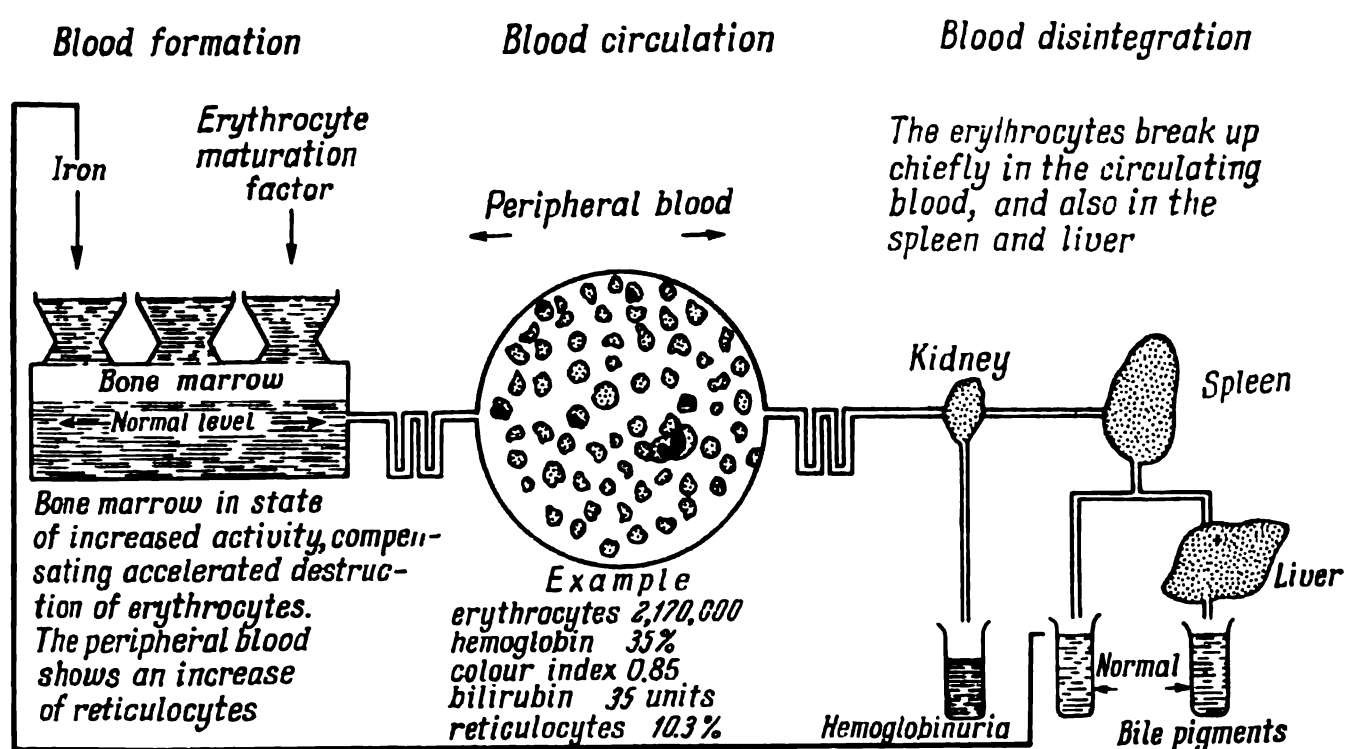


Fig. 16. Schematic depiction of pathogenesis of blackwater fever (malarial hemoglobinuria)

spirochetes, chlamydozoans and so forth; however, at present the parasitogenic theory has been completely abandoned. The formation of the disease was likewise associated with acidosis, hepatic lesions and other causes. Present consensus of opinion is that its onset is due to two causative factors: malaria and a secondary factor that provokes the hemoglobinuria, most frequently quinine, although sulfonamides, pyramidon, methylene blue, or quinacrine may do the same; moreover, attacks of hemoglobinuric fever may develop in malaria patients without any medicinal provocation (Fig. 16).

The anaphylactoid nature of the condition is witnessed by the violent onset of symptoms within several minutes after the ingestion of quinine. Evidently what occurs is that the erythrocytes decomposed by the invading parasites and subjected to the action of the haptens in the ingested medicinal preparations turn into alien antigens that immunise the organism, causing autoimmune bodies (amboceptors) to develop in it. These amboceptors or sensitisers combine with the serum complement in inducing a most violent hemolysis of the patient's red blood cells. It has been established that when the hemoglobin concentration in the plasma is high (100-140 mg/per cent) hemoglobinuria develops (term proposed by Murry and Lichtheim, 1878). In cases of hemoglobinemia the serum is light pink and spectroscopic examination shows lines characteristic of hemoglobin, oxyhemoglobin and methemoglobin. Hemoglobinuria may likewise appear in the absence of hemoglobinemia as a result of the dissociation of the blood in the renal vessels.

The jaundice should not appear at the initial stages of the hemoglobinuric fever, since intravascular hemolysis is predominant in this condition; however, the free hemoglobin circulating in the blood is captured by the reticuloendothelial cells of the liver, spleen, lymph nodes, and other organs and is transformed into bilirubin, resulting in a more or less pronounced jaundice. Urinalysis shows, besides oxyhemoglobin, a high methemoglobin content, and sometimes also an increased amount of hematin; albuminuria, urobilinuria and bilirubinuria are always observed, in most cases very markedly (the bilirubinuria is the result of a secondary parenchymatous hepatitis). As a rule the urine sediment shows lumps and crumbling yellow masses of amorphous hemoglobin, occasionally a small number of intact or lixiviated erythrocytes, frequently hyaline and granular casts.

*Clinical findings.* The passage of urine coloured like dark beer or red wine is the basic symptom of hemoglobinuria; the colouring is due to the presence in the freshly voided urine of oxyhemoglobin and on standing — of methemoglobin. (Fig. 17). In addition hemosiderin and urobilin are also assayed. After standing for a while the urine separates into two layers, the upper of which is wine-coloured and transparent, the lower dark-brown, turbid, containing detritus. The onset of hemoglobinuria is sudden; it is accompanied by chills and fever (up to 40°C and even higher), muscular and arthritic pains, adynamia, vomiting of dark, pleiochromatic bile, headache. The development of anemia and appearance of jaundice

are very rapid. The erythrocyte count falls to 1,000,000, the hemoglobin content to 3 g% (18-20 units). Leukocytosis associated with neutrophilia and monocytosis is observed; in the bone marrow myeloid and erythroblastic reactions with signs of erythrophagocytosis are seen (V. V. Nesmelova and Z. V. Taranukhina, 1956), which prove the development of intracellular hemolysis and explain the jaundice accompanying malarial hemoglobinuria. Notwithstanding active malaria the plasmodia are not demonstrable in this condition, as the invaded red blood cells are the first to disintegrate. The spleen and liver are enlarged and sensitive. *Mild, moderate, and severe forms* of the disease are recognised. The first is marked by subfebrile temperature and transitory hemoglobinuria, the last by intensive decomposition of the blood, hemorrhagic symptoms, jaundice, collapse, and anuresis. Lethal terminations were very common in the past (over 50 per cent); modern therapy has cut them down to 15-20 per cent. Death occurs as the result of shock, acute anoxia, or azotemic uremia (in cases of prolonged anuresis). Favourable courses terminate within 3-5 days when the urine recovers its normal aspect, the fever subsides and blood reparation occurs; the latter is characterised by a high reticulocyte count. Blackwater fever convalescents are subject to repeated attacks, evoked by the same agent (quinine). Cases have been described in which 2-3 attacks were registered after a lapse of 6-8 years.

*Pathological findings* vary depending on the duration of the attack. In acute cases the following are observed: icterus of the skin and internal organs, enlarged, blood-congested, dark reddish-brown spleen, enlarged yellow-brown liver, slightly enlarged, edematous kidneys with macroscopic blackish-brown striation of the renal pyramids (straight tubules full of hemoglobin casts). In more protracted cases of the disease the organs are anemic. Microscopy: the renal capillaries and splenic sinuses are clogged with the detritus formed as a result of decomposition of the erythrocytes; an excessive amount of hemosiderin and hematin are found in the hepatic cells, the sinusoidal endothelium, and the macrophages of the spleen and bone marrow; a fine granular disintegration associated with exudation is observed in the cavities of the glomerular capsules; the epithelium of the convoluted tubules is turbidly edematous and necrotic; in the lumens of these tubules finely-grained casts are found which react positively to iron (Fig. 21).

### **The gastrointestinal form**

This condition is characterised by a superimposition of marked gastrointestinal disorders over the typical pattern of malarial paroxysms; these disorders are mostly enterocolitis or gastroenterocolitis (with vomiting and diarrhea), resembling the clinical aspect of septicemic salmonellosis.

A. L. Myasnikov (1936) designates the existence of malarial hemorrhagic colitis, R. A. Luriya — even of malarial dysentery.

The most serious argument in favour of the possibility of the existence of an etiologic connection between malaria and intestinal disorders is the

occasional discovery of aggregations of malaria parasites in the intestinal vessels, but this is a general rule for the localisation of the plasmodia.

The general impressions of post-mortem examinations easily lead one to conclude that there is a certain kind of dependency between malaria and the intestinal diseases so abundant in the south.

Chronic ulcerative colitis is generally widespread in southern areas and combines with a number of other chronic ailments; however, a profound study made by the authors back in 1932 proved its independent nature: the colitis turned out to be chronic bacterial dysentery. This was confirmed by M. V. Voyno-Yasenetsky (1950) in studies of post-mortem material.

In the 627 cases in which lesions of the large intestine were discovered at autopsy cultures of small pieces of the intestinal wall were made (the tissue was minced and triturated with physiologic saline solution); it was discovered that 85 per cent of the acute cases of colitis (from catarrhal to fibrinous), whether in conjunction with malaria or not, yielded growths of dysentery bacilli.

The frequent combination of malaria and colitis is explained by the coincidence of the seasonal curves of these infections in warm climates.

Our observations have shown that colitis is most frequent in cases of persistently recurring malaria in asthenic patients showing marked vitamin deficiencies. The diarrhea intensifies during the fever relapses, causing certain authors to explain it by the intestine being allegedly infected with a malaria "virus".

However, it follows from what we have said before that the majority of such cases are simply the result of a combination of malaria with dysentery or protozoan invasions of the intestine (amebic dysentery).

There do undeniably exist so-called allergic diarrheas accompanying acute malarial paroxysms caused by an acute edematous-exudative process in the intestine. This type of diarrhea may in exceptional cases be of a hemorrhagic nature. Frequently the diarrhea is combined with other allergic components of malaria — urticaria and sharp abdominal pains that may be due to toxic processes in the serous sheath of the intestine.

Particularly grave is the condition of malarial patients who develop a semblance of acute toxoinfection.

### **Hemorrhagic forms**

Severe forms of malaria (predominantly malaria falciparum) are sometimes accompanied by hemorrhagic symptoms.

Data has been published on cases (also observed by the authors) of hemorrhagic malaria with hemorrhages in the skin, conjunctiva, retina, bleeding from the nose, mouth, and uterus, hemorrhagic vomitus, etc.

These syndromes may evidently be the result of the malarial infection, although, as we have had occasion to observe, malaria can provoke a latent course of Werlhof's disease (idiopathic thrombocytopenic purpura).

The pathogenesis of the majority of cases of hemorrhagic malaria proceeding with a normal thrombocyte count may be traced to vascular pathology.

This concept is supported by histological data. I. I. Shirokogorov (1932) discovered peculiar changes in the vascular endothelium in malaria. In describing hemorrhagic forms of malaria he noted dilatation of the blood vessels, ruptures, extravasation and perivascular infiltration in the papillary layer. The same author also described internal hemorrhages, mostly in the brain tissue, as well as small ecchymoses and extensive hemorrhages in the serous coat of the gastrointestinal tract, in the kidneys, the adrenal glands, etc.

### **Comatose malaria**

Comatose malaria is the classical form of pernicious malaria, encountered mainly in warm climates. Most of the cases of comatose forms (95 per cent) are observed in falciparum malaria in September-October in fresh, untreated cases. Certain circumstances (epidemic outbreak among a weakened population) evoke comatose conditions in tertian malaria.

Three phases are distinguished in this disease: 1) *somnolence (precomatose)*; 2) *stupor*—a deeper somnolence with only weak signs of consciousness; 3) *deep coma*—the patient is completely unconscious. In the somnolent state the patient reveals some signs of consciousness, answers questions coherently, reacts to various stimulants. Patients in a state of deep coma react to nothing and are absolutely prostrated.

*Psychoneurotic status.* In the precomatose period the majority of patients show signs of mental depression and various degrees of unconsciousness intermittent with clarity. The patient usually lies motionless; from time to time an expression of pain appears on his face, sometimes he answers questions in monosyllables, but immediately returns to a state of inhibition.

In some patients varying degrees of symptoms of psychic or motor excitation are observed. These symptoms are usually manifested upon transition of the somnolent state to coma by slight motor and psychic anxiety (mumbling broken words, groaning, throwing out the arms and legs, resistance to passive manipulations, biting down on a spoon, etc.). Upon exacerbation during coma or departure from this state the psychic and motor anxiety reactions are much stronger; long weeping fits and sudden outcries are observed.

In some instances of malarial coma convulsive jerks, clonic and even tetanic spasms occur. The authors have observed general epileptoid attacks during the first day of the comatose condition.

The convulsive attacks are much more frequently displayed at later periods of the disease, their frequency increasing in the agonal period to the status of epilepsy (F. M. Lisitsa, 1953).

*Pseudomeningeal symptoms.* Rigidity of the neck and Kernig's sign are exhibited quite early by many patients in the comatose state. These manifestations are usually looked upon as meningeal symptoms. Their ap-

pearance is due chiefly to edematous and other circulatory disturbances in the cerebral meninges, but in coma meningeal symptoms are also the result of changes occurring in various structures, among them the frontal formations regulating muscular tonus. This is confirmed by the observations of a number of authors (I. I. Shirokogorov, 1932; M. V. Voino-Yasensky, 1945) who discovered no morphologic changes in the brain meninges in lethal cases of malaria in which meningeal symptoms had been diagnosed during life.

F. M. Lisitsa (1953) described various tonic reflexes, e. g., the labyrinthine reflex in the eyes. This reflex is manifested by the counter-rotation of the eyeballs in response to a passive turning of the head. The reflex disappears with the first signs of general improvement. According to experimental data the centre of these reflexes lies in the brain stem.

The reflexes pathognomonic of coma are the initial increase of tendon reflexes, the appearance of clonic spasms and, later, their disappearance. The pupillary reflex to light may remain normal or decelerate, at a later stage it may disappear altogether.

The first of the skin reflexes to disappear and the last to be recovered are the abdominal reflexes.

Pathology of the pyramidal tract is demonstrated by asymmetry in the tonus of the mimetic muscles, and by clonic spasms; sometimes Babinski's sign or, rarely, Rossolimo's reflex are present.

Moreover, malarial coma is attended by marked lesion in the autonomic nervous system; this is associated with pathological processes in the tuber cinereum and the vagal nuclei.

Spinal fluid tension is normal or slightly elevated. The fluid is clear, containing 0.15-0.2 g/per cent protein. Solitary leukocytes are found in the sediment.

*Cardiovascular symptoms.* Tachycardia. Arterial pressure is low (90/60 mm), falling to 60/40 in the agonal period. The heart sounds are dulled, the heart dilated. The volume of blood in circulation gradually decreases towards the end of the disease.

*Respiratory system.* In severe cases accelerated respiration of the Cheyne-Stokes or Biot type is observed.

*Gastrointestinal tract.* Dry tongue, impaired deglutition, vomiting, at times diarrhea resembling enterocolitis.

The aspect of the *liver* and *spleen* are typical of ordinary malaria. In some cases the spleen is non-reactive (only slightly enlarged in severe states of coma).

*P. falciparum* ring forms and gametocytes are demonstrated in large numbers in the blood; occasionally merulation (trophozoitic) and monocyte-pigmentophages are observed.

At the height of the comatose condition the ESR is usually accelerated (60-70 mm). The white blood count shows leukopenia in the majority of patients, but cases have been described in which a moderate leukocytosis (9,000-12,000) was observed, while in solitary fatal cases of coma the authors have seen hyperleukocytosis (20,000).

Neutropenia is frequently observed in the differential white blood count, as well as monocytosis and occasionally a moderate degree of neutrophilia.

*Pathogenesis.* The basic cause of coma is the mechanical obstruction of a great number of cerebral capillaries by thrombi causing organic lesions in the brain, owing to impairment of circulation and nutrition. This interpretation of malarial coma is confirmed by pathohistological



Fig. 18. Brain in comatose malaria

examinations, during which the following changes were found in the brain in coma: hyperemia of the meninges, edema of the brain matter, presence of parasitic thrombi, capillary stasis accompanied by the formation of perivascular necrotic sites and glial accumulations around them, petechial spots in the substance of the cerebral hemispheres and the cortex of the cerebellum (Fig. 18). M. V. Voino-Yasenetsky (1945) established, during long-term investigations in Tajikistan, that malarial coma never occurs in the absence of parasitic stasis and thrombosis; however, V. S. Sadoyan et al. (1955) consider these thrombi to be post-mortem formations, while A. A. Gontayeva (1953), N. K. Bogolepov (1950, 1958) and other authors hold that the mechanism of coma and its symptoms is allergic (neurotoxic). In a number of fatal cases the authors were not able to demonstrate the above morphological changes in the brain, although severe malarial coma had been diagnosed during life.

Proceeding from the above, a number of authors have attempted to allot a prominent part in the development of coma to the virulence of the malaria plasmodia, reflected in their toxic effect on the organism as a whole, including the brain. These authors point out an important circumstance, namely, that coma is as a rule a condition observed in falciparum



malaria (the more malignant form of the disease). However, reports have been made on the development of coma in benign tertian malaria.

We consider that a great part in the pathogenesis of malarial coma is played by immunogenic hyperergia (without thrombosis in the capillaries of the brain), a condition manifested by hemorrhagic encephalitis, marked swelling of the brain substance, cerebral and meningeal edema accompanied by disturbances in cerebral circulation and nutrition, and the development of focal changes in the brain.

*Prognosis* for malarial coma is always very grave. Lethal terminations occur, on the average, in 40 per cent of cases. Particularly grave is the prognosis in cases of undernourished subjects. When treatment is instituted in the precomatose stage (nascent somnolence) vigorous therapeutic measures effect complete recovery.

### Other forms of cerebral malaria

The comatose condition is not always typical; it is not always possible to determine the character of the sensorial disturbance although the condition is a dangerous one owing to the development of other threatening symptoms of an acute toxic involvement of the brain. It is not without reason that medical practitioners, coiners of the term "acute abdomen", also widely employ the concept "cerebral malaria". Such a bedside diagnosis must attract attention not only to signs of coma, but also to other no less important and life-threatening symptoms of cerebral malaria.

In accordance with the mechanism of their formation certain other forms of malaria may be included in the cerebral group. Among them are the *adynamic form of malaria*, characterised by an extremely severe general debility and decrease of vascular tonus, and the apoplectic form, characterised by syncope, weak pulse and sudden death. The so-called *algid form* occupies a place by itself. While it does not always feature coma, and consciousness may be retained, the patient lies in a state of deep collapse and prostration, his temperature falls below normal (35-35.5°C), the pulse is thready, sometimes imperceptible. The facial expression conforms to the well-known facies hippocratica; the patient is indifferent to his surroundings; his features sharpen, eyes sink, nose, lips and fingers become cyanotic; great drops of cold, clammy sweat appear on his face, his body is cold to the touch. In algid malaria the tendon reflexes are weakened or absent.

Algid malaria is considered hopeless. The authors have observed the violent speed of this affliction: patients with malignant tertian malaria in whom coma had appeared in the daytime died by evening with typical algid symptoms.

Another manifestation of cerebral malaria is hemorrhage in the brain — from petechia to marked hemorrhages that are occasionally observed in severe cases of malaria. Marchoux (1926) cites a fatal case with extensive hemorrhage in the cerebellum. I. I. Shirokogorov (1932) describes four cases of softening of the brain caused by malarial hemorrhage sustained



at an early age. It seems to us that extensive bleeding into the brain matter is an extremely rare incidence in malaria, and the majority of cases described at an advanced age should rather be connected with already existing atheromatous developments in the vessels.

Reports have also been published on the development of acute ataxia (Leyden-Westphal ataxia).

Conjointly with other already described forms of very severe malaria (the typhoid-like, hemorrhagic, bilious and other forms) cerebral malaria comprises the extensive group of *pernicious malaria*. These forms of the disease may be looked upon as being urgent conditions. This prompts the medical practitioner to apply the most rapid therapeutic measures. Early, vigorous, and efficient therapy of pernicious forms of malaria lower the percentage of lethality. Upon the slightest suspicion of pernicious malaria not a minute must be lost; waiting for the result of blood tests, evacuation of the patient over long distances without treatment may be the cause of his death.

Periods of national calamities (wars, etc.) are usually attended by extensive outbursts of malaria, and what is more, the character of the malarial infection changes, a great number of malignant forms appear owing to decreased immunity in the population at large, to the transportation to new localities of strains of the infection against which the local population is not immune, to bad management, etc.

### **Acute malarial psychoses**

Mental disorders resulting from malaria have been known for ages and have been described by many authors.

Malarial psychotic disorders are divided into *initial psychoses* of a toxoinfectious nature appearing in acute and protracted malaria (but only during the period of feverish paroxysms), and *secondary psychoses* during which the mental disorder appears in the afebrile period, often after convalescence from a severe and prolonged course of malaria; this latter group of disorders may be placed among the postmalarial psychoses, when malaria is a factor conducive to the development of hereditary or constitutional mental disorders.

#### *Psychopathologic syndromes of malaria:*

1) initial malarial mental disorders: acute feverish delirium, occasionally amentia, epileptoid excitement, maniac conditions, psychotic disorders in cerebral forms of malaria;

2) secondary malarial mental disorders: mental weakness, amentia, schizophrenic syndrome, dementia, amnesia, depression, personality changes, inhibition of mental development, neurasthenia, hysteria;

3) hereditary or constitutional mental disorders evoked or provoked by malaria: schizophrenic reaction, epilepsy, cyclothymosis, etc.

This scheme is acceptable in principle, but we must warn against the fascination it has for many authors who tend to ascribe to malaria a too

great—almost universal—role in the onset of various mental conditions.

Prognosis for exogenic malarial mental disorders, as for other toxinflectional psychoses, is good. The most frequent termination is complete recovery (simultaneously with recovery from malaria). Prognosis for afflictions in which malaria was only an incitement for the development of endogenous (hereditary, constitutional) psychoses is questionable.

## LESIONS OF SYSTEMS AND ORGANS IN MALARIA

### The blood and the hematopoietic system

Malaria is above all a disease of the erythrocytes, thus the changes occurring in the red blood. Multitudinous invasion of the red blood cells and their resultant disintegration are the most important pathogenetic factor in the onset of malarial anemia. The number of plasmodia in the blood varies; in some cases they are demonstrated with difficulty, in others there are so many that they are discovered immediately—several parasites are found in every field of vision.

Reports have been published on the presence of malaria plasmodia in 30 to 50 per cent of all the erythrocytes. All such cases were fatal.

*The pathogenesis of anemia associated with malaria* may be interpreted not only by the destructive effect of the parasites invading the erythrocytes. Hemolysis is conditioned by other factors as well, as in many cases where the plasmodia are discovered with great difficulty the anemia is very pronounced (15-20 per cent hemoglobin). In this connection the development of immunohematologic factors (autoisoagglutinins) must be taken into consideration, as well as the part played by the hyperplastic organs of the reticuloendothelial system (the spleen, liver, etc.) that intensify the hemolysis of the invaded erythrocytes.

Inhibition of the bone marrow function of blood-formation by the hypersplenic factors developed in the enlarged spleen also plays its part in the progressive course of anemia.

Similar to paroxysms of freshly contracted malaria the protracted course of malaria is associated with a decrease in the absolute number of neutrophils—neutropenia, relative lymphocytosis, and monocytosis. During the apyrexial period of protracted malaria leukopenia together with relative lymphocytosis and monocytosis is usually observed (Y. I. Novosylova, 1956). In pernicious malaria, particularly in cases of malarial coma, leukocytosis and neutrophilia are occasionally noted.

Certain authors and medical practitioners tend to overestimate the diagnostic value of lymphocytosis and monocytosis in malaria. The present authors wish to stress the fallacy of such an interpretation. A study of the leukocyte counts charted by S. D. Moshkovsky makes it clear that there is no absolute lymphocytosis nor monocytosis: absolute monocytosis is only present in very heavy infections. Moreover, similar differential white blood counts are observed in a number of other infections.

The differential white count alone, without parasitologic confirmation, does not indicate malaria; a most deplorable mistake is made by physicians who diagnose malaria only on the basis of differential blood counts and administer treatment accordingly.

### **The spleen**

Enlargement of the spleen is one of the cardinal symptoms of malaria, most important in diagnosing this disease and in evaluating its response to specific therapy (Fig. 19).



Fig. 19. Splenomegaly in malaria

In protracted cases of malaria the dimensions of the spleen are often associated with the duration of the malarial process. The spleen is then usually firm and painful.

It seems to be the prevailing opinion among the majority of authors that falciparum malaria causes a lesser enlargement of the spleen than do other forms. This is to a certain degree true of the acute period of the disease; however, in the protracted period falciparum malaria is also often accompanied by a high splenic rate. The hepatolienal syndrome is most frequently observed. Often anemia and leukopenia are found simultaneously in such patients, in connection with hypersplenism, owing to increased hemolysis and bone marrow inhibition. During this period the process is connected with the vital activities of the plasmodia, and proper treatment makes it reversible.

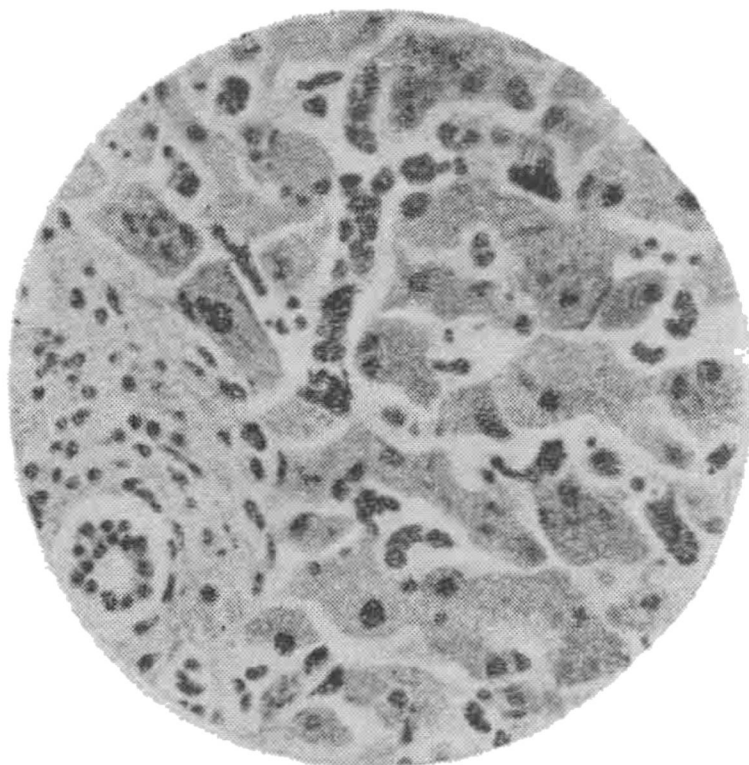
Other hepatolienal symptoms observed are subfebrile temperature, occasionally distention of the abdomen and diarrhea of portal origin, still

rarer a slight ascitic condition associated with disturbance of the fluid balance function of the liver owing to cellular lesions (portahepatic hypertonicity).

Among the grave complications of splenomegaly in warm climates the most dangerous one is rupture of the spleen, more common in acute cases; ruptures in cases of chronic splenomegaly are rarer owing to the formation of firm adhesions around the spleen.

### **The liver**

The liver reacts to acute attacks of malaria by significant enlargement, and this condition may remain for a considerable time, occasionally even after the paroxysms have responded to treatment.



**Fig. 20. Liver in malaria. Abundance of pigment in reticuloendothelial cells**

Positive palpation of the rim of the right hepatic lobe was noted by the present authors in 178 of 316 patients (56.3 per cent), but painfulness of the most accessible for palpation left lobe is a constant symptom of malaria. Sometimes the enlargement is quite considerable, and the liver is very firm.

In protracted cases of malaria mesenchymal hepatitis is more frequent, in association with jaundice and dysfunction of the hepatic cells (Fig. 20). A description of a primary malarial dystrophy of the liver has been published by P.A. Tepper (1935). A process of a different type, with hypertrophy of the liver and ascites, was described by A.N. Kryukov (1924).

Evidently hypertensiveness of the portal system and ascites are connected with a disturbance of the function of fluid metabolism in the hepatic

cells. The paramalarial process is reversed by adequate therapy and the organ is restored to its normal condition. However, in some cases of interstitial hepatitis complete reparation is not attained. In unfavourable conditions processes of this type may provoke the development of cirrhosis of the liver (the latter is discussed in the section on metamalarial diseases).

### **The gastrointestinal tract**

Malaria often involves the gastrointestinal tract. In the protracted period subacidic and anacidic gastropathies are most frequently observed. Intestinal disturbances are displayed by abundant watery, mucous stools of the enterocolitis type. However, our observations have shown that this loosening of the bowels occurs predominantly in weakened, starved, avitaminised patients and may often be traced to a dysenterial infection (dysenterial ulcerative colitis).

### **The cardiovascular system**

A number of grave circulatory disturbances are observed during paroxysms. The pulse usually corresponds to the temperature, but occasionally a pulse lag is noted. In mild cases the cardiovascular condition in malaria is that of infection hypotonicity.

During the paroxysms a dullness of the heart sounds is noted, often concomitant with a systolic murmur at the apex and base of the heart. The volume of the blood in circulation and its velocity are increased during the feverish attack (Y. M. Tareyev, 1943).

The clinical pattern of cardiac involvement is very characteristic in severe cases of protracted malaria in weakened, anemic, and inadequately treated patients; these forms of the disease are very typical of colonial countries with torrid climates.

Auscultative and generalised clinical symptoms highly resemble the symptoms of valvular heart failure, sometimes circulatory deficiencies are present. Dynamic follow-ups of patients in whom all the above symptoms disappear upon convalescence in a remarkably short time provide a final confirmation of the accuracy of the conclusion that the circulatory disturbance is of muscular origin.

Electrocardiographic investigations demonstrate myodystrophic changes in the heart.

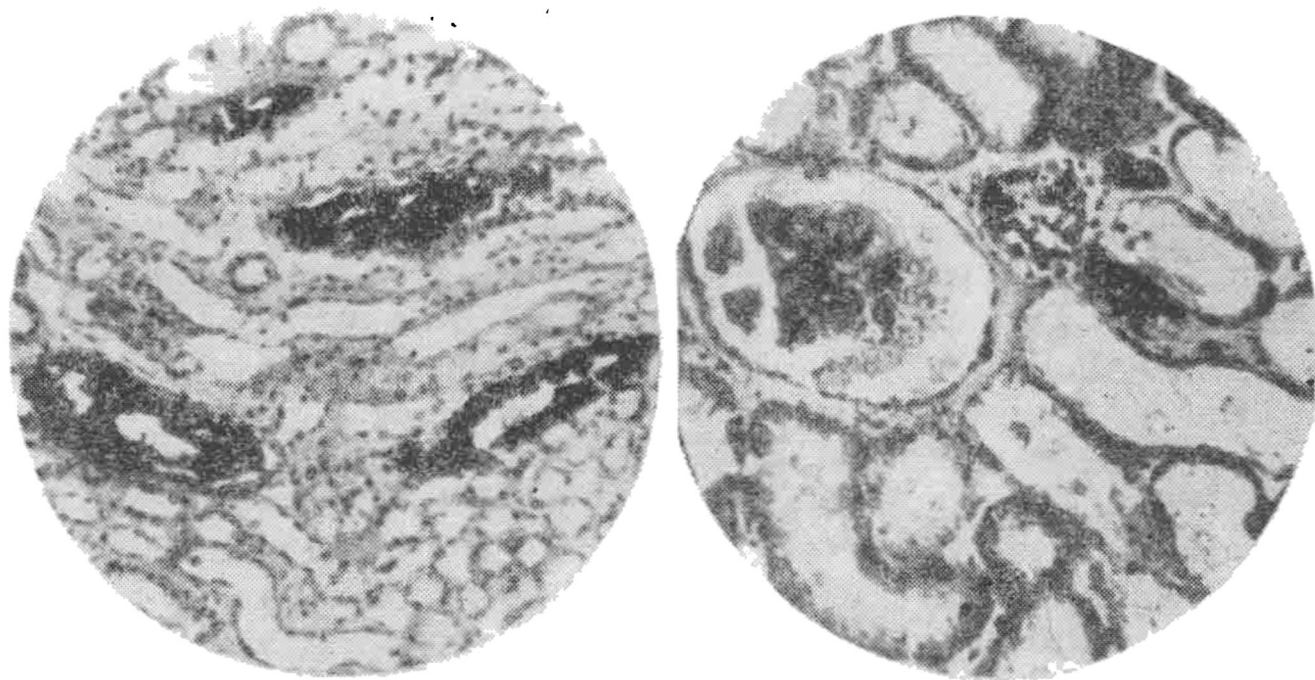
### **The kidneys**

The usual febrile albuminuria ("renal reaction") is quite frequently noted in malaria, but it is of a transient nature.

A lesion most typical of malaria is acute nephritis. According to Y. M. Tareyev this condition is observed in only 1-2 per cent of vivax cases, in falciparum malaria it is more frequent — up to 10 per cent of all cases. True nephritis associated with malaria usually presents the complete characteristic quadruplet: hypertension, albuminuria, hematuria and edema.

Prognosis for acute malarial nephritis is generally favourable. Malarial nephritis quickly responds to specific treatment, the edema and all morbid symptoms disappear quite soon. It is in comparatively rare cases that nephritis of this type develops into a chronic metamalarial nephritis.

The specificity of malarial nephritis is undeniable, although it is not directly connected with the localisation of the plasmodia in the kidneys, but is due to the general toxico-allergic reaction in the blood vessels and renal parenchyma.



**Fig. 21.** Kidney in blackwater fever (the left illustration shows low magnification, the right high magnification). Convoluted tubules are dilated; their epithelium is seen to be in a state of opaque swelling and necrosis; fine-grained disintegration with exudation is seen in the cavity of the glomerular capsule

However, besides the decisive part played by malaria in the induction of the nephropathic condition, other important conducive factors are physical exhaustion, starvation and cold.

Besides nephritis, malaria may also bring on a syndrome of lipid nephrosis. According to Y. M. Tareyev this is actually a lipid-amyloid nephrosis or a nephrotic type of chronic nephritis, and only in exceptional cases is the pure form of lipid nephrosis encountered. Malarial lipid nephrosis is predominantly observed in quartan malaria.

### **Malarial edema**

So-called malarial edema develops, as a rule, in severe cases, particularly protracted ones. The edema begins with the face and eyelids, then appears on the legs, but most commonly it makes a simultaneous appearance everywhere. A slight degree of ascites is likewise observed. Urinalysis and volume of urine passed show no noticeable deviations from normal.

At present the majority of authors recognise starvation as the principal cause of edema in malaria. The fact that classic malaria in colonial countries, particularly in the past, was very frequently complicated by edema is another confirmation of this point.

The present authors affirm, on the grounds of their personal data (1921-1923), that the edema is prevailingly not the result of malaria, but of alimentary dystrophy, the edematous symptoms of which increase under the influence of the malarial infection.

In the overwhelming majority of cases specific treatment and proper diet cause the edema to resolve.

### **Lesions of the nervous system in protracted cases of malaria**

The diverse nervous and mental syndromes described by many authors for chronic malaria are observed very rarely and their origin is not always of a malarial nature. They are frequently based on other exogenous or endogenous factors and their coincidence with malaria is merely accidental, or malaria only provokes and accelerates the process.

Neurological syndromes in lesions of the central nervous system are quite diversified, comprising the subject of special manuals. These syndromes are acute malarial tremor, pyramidal and extrapyramidal hyperkinesis, acute ataxia (Leyden-Westphal ataxia), disseminated myelitis, cerebral hemorrhage (in hemorrhagic malaria), etc.

Lesions of the peripheral neurons in the form of neuralgias and neuritis as well as disturbances of the autonomic nervous system are mostly observed in chronic malaria. However, the connections between malaria and the neuralgia or neuritis can be proved only in very rare instances. Malarial neuralgia and neuritis involve various nerve stems.

Lesions of the *autonomic nervous system* associated with malaria are not specific (postmalarial vegetative disturbances). These disturbances are manifested by excessive perspiration, angiospasm, chilliness, headache, etc.

### **Ophthalmic lesions**

In warm climates malaria is more frequently complicated by eye involvement than in the temperate zones.

Mostly the cornea is affected: various authors have described superficial keratitis and serpiginous ulcers. Iritis, iridocyclitis and opacification of the vitreous, neuritis of the optic nerve, retinochoroiditis and hemorrhage of the retina are less common.

In diagnosis it is extremely important to differentiate between malarial lesions of the eye and ophthalmic complications associated with chemotherapeutic toxicosis (quinine and plasmocid).



## **Ear trouble**

The malarial infection evokes all manner of alterations in the vascular and nervous systems, therefore it also involves the delicate vasoneural structures of the organ of hearing. Moreover, the effect produced on hearing by quinine is well known.

Circumstantial studies of the pathology of the auditory analyser in tertian and falciparum (Bokhara variety) infections were carried out in the Soviet Union by E. A. Ladyzhenskaya (1958), a specialist in otoneurology; she found that falciparum malaria affects hearing more often than the tertian infection does, and that vestibular involvement is more common than cochlear. The vestibular symptoms are disguised by vegetative disturbances (vertigo, a buzzing in the head, temporary deafness). In cerebral forms of malaria (coma, hypertoxic condition) the generalised cerebral disturbances are accompanied by impairment of the vestibular apparatus.

Impairment of hearing evoked by acrichin (quinacrine) has more commonly been observed to develop as a result of overdoses of this preparation while quinine has an elective toxic effect on the VIII (acoustic) pair of cranial nerves.

In so far as it is impossible in many cases to establish the true cause of neuritis of the VIII pair of cranial nerves by clinical findings the only practical recommendation that can be made is to substitute quinacrine for quinine in patients in whom impairment of hearing is noted.

## **METAMALARIAL DISEASES**

There is no sequelae to malaria in the overwhelming majority of cases, but occasionally, particularly if treatment was inadequate, and also owing to individual reactivity, the disease leaves stable and quite profound organic or systemic lesions.

First place among metamalarial disorders is taken by anemia. Post-malarial anemia may be the result of organic or functional bone marrow deficiencies. The former is exceptionally rare, the latter is more frequent (as confirmed by bone marrow pictures in smears obtained from malaria patients). Anemia is often the outcome of postmalarial processes in the hepatolienal system.

The malarial origin of chronic metamalarial splenitis in tropical and warm climates is undeniable.

The obligatory symptoms by which this syndrome was diagnosed until quite recently were the precise pathohistologic picture pointed out by Banti (splenic adenofibrosis) and autochthonous development of the disease (absence of malaria and syphilis in the anamnesis). These requirements have now been rejected, in so far as the Banti pathohistologic basis has proved to be very rare, while malaria and syphilis are frequent causative factors leading to the development of this disease.

The above splenetic conditions are associated with the malarial infection; however, when the patient has already been cured of malaria the



conditions persist, progressing to degrees of splenomegaly when the spleen reaches the small pelvis.

In the tropics splenomegaly in the untreated and undernourished indigenous population (Malays, Negroes, etc.) is accompanied by acute cachectic conditions (terminal postmalarial cachexia).

The development of hypersplenism with pancytopenia has been observed in the course of a malarial infection.

The clinical and pathomorphological types of splenopathy are diverse: hepatolienal or splenetic hemorrhagic syndromes may be encountered as well as pure thrombosis of the splenetic veins with no cirrhosis of the liver. In certain cases the feverish paroxysms associated with splenomegaly itself, particularly with its thrombophlebitic form, are mistaken for manifestation of the malarial infection and are treated accordingly — with no results.

Another postmalarial disease is metamalarial hemolytic jaundice (macroplanocytic acquired hemolytic jaundice or the Hayem-Widal-Abrami disease). This disease is not always accompanied by significant splenomegaly, but in the majority of cases the spleen grows to enormous dimensions. Since immunohematologic factors play an important part in the pathogenesis of the hemolysis occurring in this form of disease (confirmed by a positive reaction to the Race-Coombs test) a good therapeutic result is obtained with prolonged administration of corticoid hormones possessing an intensive anti-allergic action.

Now a few words about postmalarial cirrhosis of the liver. This disorder may develop as a unitary process, but a hepatolienal syndrome is more frequently observed. Occasionally the cirrhosis is of a hypertrophic nature, in other cases it may be of mixed origin. Some authors doubt the malarial genesis of cirrhosis. An obstacle in the way of the true solution of this problem is the fact that not a single morphologic change in the liver of a malaria patient can be indisputably considered of malarial origin: it is quite possible that a person who is already afflicted by cirrhosis of the liver may contract malaria; this possible latent form of cirrhosis may be aggravated and provoked to further development by the malarial infection.

V. A. Tarnogradsky (1938) reported that in endemic sites of malaria in Azerbaijan cirrhosis of the liver was very widespread. I. I. Shirokogorov (1932) ascribed the frequency of cirrhosis of the liver in Azerbaijan to its malarial origin.

The development of malarial cirrhosis was proved by P. A. Tepper (1935). Among the cases of combined malaria and portal cirrhosis observed by him in Samarkand the diagnosis was checked on two occasions by autopsy and histological preparations; the malarial etiology of the cirrhosis was confirmed in these cases by certain features in the course of the disease and its clinical and pathologic aspects.

The majority of Indian authors explain the high incidence of cirrhosis in that country by the high malaria rate, and inadequate treatment. The same conclusion has been reached concerning the frequency of cirrhosis in the West Indies. Emphasis has been laid of late on the conducive part

played by vitamin B<sub>1</sub> deficiency and malnutrition in the formation of malarial cirrhosis.

A similar type of decompositional disorder is the postmalarial (terminal) cachexia encountered in colonial countries in association with many tropical diseases (trypanosomiasis, kala-azar). Photographs of such patients are traditionally included in all foreign manuals on diseases of torrid climates. These conditions are not connected with the vital activity of the plasmodia.

The authors' personal experience has convinced them that it is highly improbable that malaria per se can bring on cachexia. This latter condition develops in malaria patients afflicted with alimentary dystrophy, avitaminosis, persistent looseness of the bowels and other complicating protracted disorders. The development of cachexial conditions are also influenced by lesions of the most important trophic and metabolic centres of the pituitary gland and the medulla, leading, as we know, to cerebro-endocrine cachexia and impairment of fluid metabolism in the tissues (exsiccation).

### MALARIA AND PREGNANCY

Almost all authors note the following: 1) frequent premature deliveries in malaria; 2) high mortality rate of the newborn; 3) graver and more persistent course of malaria in pregnant women (personal observations); 4) the appearance of pertinacious relapses toward the end of the pregnancy and after confinement (personal observations).

Thus Clark (1915), having observed 107 fatal cases of malignant (*falciparum*) malaria in Ancon, reported that of 24 adult female patients 12 died during pregnancy or shortly after childbirth. According to the data of Wickramasuriya (1937) for Ceylon, where the public health service is very inadequate, of 170 non-pregnant malaria patients 11 died (6.4 per cent), while of 358 pregnant malaria patients 47 succumbed (13.12 per cent).

The severe course of malaria in pregnancy and its high mortality are due to heightened reactivity of the organism during this period. This also explains the pronounced and variegated visceral pathology observed in pregnant malaria patients: here we have high degrees of anemia, greatly enlarged spleens, occasionally jaundice, edema, and so forth. Malaria in pregnancy is resistant to medication and the severe symptoms of this infection clear up more slowly.

A certain factor in the severity of the course of malaria in pregnant women is inadequate, irregular treatment, and in some cases also an erroneous fear of administering antimalaria preparations during pregnancy; owing to this fear the patient is given insufficient doses of medicine and the course of treatment is shortened. However, it has been known for long that in the absence of treatment, or when treatment is inadequate, malaria may often be the cause of premature delivery and of the death of the fetus.

M. V. Voino-Yasenetsky (1940) cites 24 cases, giving the duration and termination of the pregnancies. In half of these cases delivery was spon-

taneous, usually shortly before the patient fell into a comatose condition, or when she had already lost consciousness. All the women were delivered of stillborn babies, except one infant who lived for 26 hours. This phenomenon — the birth of unviable babies—has been noted by other authors as well.

Labour was frequently protracted, and the postconfinement period was a severe one.

Thus, as observed by Wickramasuriya (Ceylon, 1937), of 253 pregnant women afflicted with falciparum malaria only 45 (17.8 per cent) were delivered at term, while in 208 (82.2 per cent) premature labour occurred; 82 infants (32.4 per cent) were stillborn, 13 fetuses succumbed prenatally together with their mothers, while 83 newborn died during the first days of life. Consequently, prenatal mortality and mortality of the newborn comprised 66.9 per cent (178 of 253).

At the same time the data on Yerevan reported by M. L. Reniger-Areshева (1944) shows the percentage of lethal cases of malaria in pregnancy to be extremely low (1.2 per cent), as systematic therapeutic and preventive measures were enacted in this city.

The above data taken from literature and personal experience lead the authors to conclude that when treatment is instituted at early stages of the malarial infection and is conducted regularly pregnancy proceeds normally and the fetus is not affected. In these conditions childbirth was normal in all observed patients.

M. V. Voino-Yasenetsky set himself the task of making a more profound study of the data in order to clarify the effect of malaria on pregnancy. During a number of years (1935-40) when the malaria rate in Tadjikistan had increased, 1,000 obstetric cases were selected for investigation; 250 of these cases were complicated by malaria and the plasmodia were demonstrated in the blood of the childbed patients. Moreover, three other groups of 250 parturient women per group were taken for comparison (Table 3).

Table 3

Effect of Malaria on the Fetus and the Newborn

Parturient women	Total number of deliveries	Number of still-born infants	Number of infants who died soon after birth	Total infant lethality, per cent
Healthy .....	250	3	5	3.2
Had malaria prior to pregnancy .....	250	5	17	8.8
Had malaria during pregnancy .....	250	15	18	13.2
Had malaria during parturition .....	250	21	35	22.4

An analysis of his data led M. V. Voino-Yasenetsky to the conclusion that malaria undoubtedly has a very unfavourable effect on the outcome of the pregnancy and the fate of the fetus, particularly active ma-

laria, with parasites present in the blood of the patient. The worst results are produced by falciparum malaria: of the 250 confined women in whom the plasmodia were discovered 135 had benign tertian malaria; among them 8 stillbirths were registered, and 16 infants died within the first week of life (lethality 15.7 per cent). In 97 cases of childbirth complicated by falciparum malaria 13 infants were stillborn, and 19 died soon after birth; the total infant mortality was 33 per cent. A high percentage of premature deliveries was established in women who had had malaria prior to the pregnancy (13.6 per cent), in women who had had malaria and recovered from it during pregnancy (15.4 per cent), in women afflicted with benign tertian malaria at the time of their confinement (24.9 per cent), and in women who suffered from the falciparum infection at childbirth (41.4 per cent).

### MALARIA IN CHILDREN

Some pediatricists consider that malaria in childhood is atypical as regards pyrexia and other symptoms. However, if we exclude malaria in infancy and early childhood (see previous chapter), there are no grounds for speaking of atypical childhood malaria, as there are likewise no grounds for speaking of atypical malaria in adults. According to the opinion of N. Y. Kushev (1925) malaria follows a mild course in childhood; according to other authors (P. P. Moufel, 1934; R. S. Gershenovich, 1947) it is either severe or runs the same course as in adults. Severe courses of malaria are observed in tropical lands where, according to the data of the Central Institute of Malaria, malaria is in the majority of cases much severer in children than in adults. Moreover, children display relapses more frequently. A multitudinous generation of parasites with a large number of gametocytes is often observed in the blood of child malaria patients.

It has rightfully been pointed out by a number of authors that in epidemic sites children are affected more frequently and with greater severity than adults; this is owing to the fact that they have not yet developed any immunity against malaria while adults have. Fresh outbreaks of malaria in new sites affect both children and adults in practically one and the same manner.

Christophers (1939) and Stephens studied a certain colonial site of malaria; they noted an overall infection among children younger than two years while among children between 2 and 5 years of age the incidence was 71.4 per cent; at the same time the malaria incidence among the adult population in this locality was only 10 per cent.

Of late reports have appeared on a specific form of tertian malaria in children living in temperate or northern zones, the so-called fulminant malignant tertian malaria (*malaria tertiana siderans*) that is most frequently observed in children from 4 to 15 years of age (very rare in adults!). This malarial infection appears in the spring both in individuals who have never formerly had malaria (after a protracted period of incubation), and in those who had it the previous summer. Since 1927 cases of sudden malignant malaria in children in the Russian Federation were observed

and described by I. V. Bystrov, G. M. Lopatin, Y. M. Tareyev and A. A. Gontayeva, A. D. Polumordvinov, the present authors, and many other investigators of malaria.

The specific features of this form of malaria are as follows. The disease begins with an ordinary feverish attack. However, severe headache and nausea with vomiting are conspicuous. On the second day the child usually feels well, plays, goes to school. The next paroxysm is of greater severity: marked cerebral symptoms are immediately apparent — intolerable headache (the patient cries out with pain), vomiting, somnolence, convulsions, sudden outcries, loss of consciousness, Cheyne-Stokes respiration; death occurs within 5-6 hours. During life the parasites of tertian malaria are discovered in small numbers in thick smears (post-mortem laboratory tests should be done within 24 hours after death, otherwise the plasmodia decompose). An interesting point is that solitary parasites are found in the brain capillaries.

The mechanism effecting rapid death in fulminant tertian malaria is most probably cerebral anoxia caused by an acute allergic swelling of the brain matter.

Sudden tertian malaria in children and adolescents requires the closest attention of all medical practitioners. Immediate treatment must be instituted in every case of acute or relapsing malarial infection in children and adolescents, particularly in the spring months.

#### DURATION OF MALARIA

Two diametrically opposite opinions concerning the duration of the malarial infection have been held until quite recently. Some authors looked upon malaria as a disease that continued for many years, and even tens of years, while others held that single infections were cured within 1-2 years after infestation.

The first opinion is based on faulty observations conducted in endemic zones where repeated infection was not excluded, on the description of doubtful, debatable cases of extremely protracted courses of malaria (over periods of 10 to 30 years) and also on the inability or lack of desire to differentiate the malarial infection from postmalarial disorders.

Sensational, extraordinary — but doubtful — cases have been cited when malaria continued for many decades, or relapses occurred after 20-40-60 years (!).

These reports are refuted by the following data cited by Y. M. Tareyev (1943) in his monograph on malaria: Gujemene and Obrène in 1934 investigated 216 individuals who had had malaria during World War I and, notwithstanding the fact that many of them presented diverse “malarial” complaints, including even paroxysms (?) of malaria, not one of them presented anemia, an enlarged spleen, plasmodia in the blood, or a positive reaction to Henry’s test. Marchoux (1926) wrote that among the soldiers who were ill with malaria in Macedonia in 1918 the number of acute manifestations of this infection after they had returned to France decreased

progressively in 1919 and particularly in 1920; by 1921 no parasites could be discovered in the blood of any of these ex-soldiers.

Of the over 600 patients treated in the Tübingen sanatorium for post-war malaria plasmodia were discovered 3-4 years later in only one patient; the others arrived with a diagnosis of malaria based on monocytosis; in a number of cases postmalarial splenomegaly was present; tonsillitis and sinusitis, tuberculosis, bronchiectasis, osteomyelitis, furunculosis, endocarditis and other conditions were erroneously taken for the sequelae of "war" malaria.

A true solution of the question of the duration of the malarial infection requires, first and foremost, prolonged epidemiologic observation and scrupulous documentation of data.

M. G. Rashina analysed extensive data accumulated over a period of 23 years; this author affirmed that the overwhelming majority (90-95 per cent) of malaria patients were cured (even in cases of incomplete courses of specific antimalaria treatment) within one year (*falciparum* malaria) and 1-2 years (*vivax*). Summarised data of the Central Institute of Malaria and Medical Parasitology obtained in various points of the Soviet Union shows that the duration of the *vivax* and *falciparum* infections is approximately uniform in the various latitudes of the U. S. S. R. (M. G. Rashina, 1937). A. I. Khovanskaya studied the data on 2,000 people subjected to prolonged medical observation (2 to 4 years); she established that the disappearance of acute attacks and afebrile latent periods (when the parasite is present but inactive) occurs in 11-12 months in 90 per cent of patients, in 13-18 months in 3.1 per cent, in 19-24 months in 3.1 per cent, and takes up to 3 years in 0.8 per cent of cases; in *falciparum* malaria symptoms of the disease disappeared before 12 months had passed. E. I. Fastovskaya (1950), working on data obtained in the southern regions of the U. S. S. R., established a still shorter duration of *falciparum* malaria — approximately six months in 96.7 per cent of cases.

The observations made by S. S. Melik-Adamyan (1939) led him to conclude that the malarial infection was overcome within 8 months in the overwhelming majority of children (88.6 per cent). However, to this period one must add the duration of the incubation period (children having a form of tertian malaria with a prolonged incubation period were observed), and then the overall duration of tertian malaria may be considered within the range of  $1\frac{1}{2}$  years.

B. P. Nikolayev (1939, 1941) made a comprehensive study of 2,137 cases of tertian malaria (of them 1,573 after prolonged incubation periods); his conclusions were that the maximum duration of the *vivax* infection (counting from the moment of infestation) was not much longer than 2 years for cases with both prolonged and short incubation periods.

In order to study the duration of the malarial infection Nikolayev made an analysis of 200 cases of experimental sporozoite tertian malaria (inoculated by mosquito bites); the subjects were placed in conditions that excluded the possibility of re-infection; Nikolayev concluded that the maximum duration of tertian malaria does not exceed 870 days.

A. Missiroli (1941) observed complete disappearance of malaria in a certain area one year after the enactment of antimalaria measures, and this led him to declare the following: "For me there exists no chronic malaria, there is only re-infection."

The greatest duration of malaria is caused by quartan malaria (3-4 and more years), and this infection is characterised by longer latent periods.

Interesting data that convincingly show the duration of malaria infections in man to be restricted to definite periods may be obtained by observation of recipients transfused with blood from donors who had in the recent past been afflicted with malaria.

We observed three such donors who had recovered from protracted, persistent, relapsing malaria infections: the first had been ill from 1937 to January of 1940 with a very severe form of tertian malaria; the second had been affected with a persistently relapsing form of tertian malaria from 1938 to 1940; the third had from 1938 to March 1940 been subject to a persistently relapsing falciparum infection contracted in Tadzhikistan.

These three patients enlisted as donors at our blood bank in 1942. Their blood was transfused to wounded soldiers (50 transfusions in all) and no malaria was registered after any of these transfusions.

Consequently, facts prove that malaria (particularly vivax and falciparum) is not as protracted a disease as was thought by the old authors; 1-1½ years is the average duration of malaria, accepted at present by the majority of researchers. As regards sporadic cases of quartan and tertian malaria, particularly in hot climates, it must be noted that 5 to 8 per cent of malaria infections are of longer than average duration.

## IMMUNITY

All people are susceptible to malaria infections; if certain individuals do not contract the disease in malaria sites this does not signify that they are unsusceptible: the disease can be passed on to them artificially through mosquitoes.

The resistance to malaria is strictly individual. Various people infected with one and the same brand of plasmodia react differently, consequently the clinical course of the infection is different in different people.

When the parasite has penetrated into the human organism the latter mobilises all its immunity resources that act in two directions: against the metabolic waste of the plasmodia and against the plasmodia themselves. During each merulation (trophozoic period) only a small part of the merozoites invade the erythrocytes, the rest perish; this must be looked upon as the result of the action of the immunogenic factors of the macro-organism. Were it not for these factors any malarial infection would terminate after several merulation (trophozoite) cycles by total invasion of all the erythrocytes and the inevitable death of the patient owing to the enormous reproductive potential of the plasmodia. Even in untreated cases the number of parasites gradually diminishes and the patient slowly recovers. As was pointed out above, cases have been observed when an indi-



vidual was host to great numbers of parasites, yet no paroxysms of malaria ensued.

Consequently, immunity against both the parasites and their metabolic products gradually increases within the course of the disease.

S. D. Moshkovsky (1952) designates this condition as concomitant immunity, while E. Sargent (1936) calls it premunition. The development of this immunity commences with the penetration of the pathogen into the patient's body. Such a patient, or plasmodia host, cannot be infected with a homologous species or brand of the parasite, but infection with a heterologous species, subspecies or brand causes the disease. So, for instance, if a certain individual is ill with tertian malaria evoked by the northern subspecies he may be infected by the southern subspecies, or with falciparum or quartan malaria.

There can be no doubt of the development of a residual or postinfectious immunity after recovery from malaria, particularly if the patient was subjected to several re-infections. However, this immunity, contrary to the immunity that develops after infections such as typhus, typhoid, scarlet fever, or measles, is unstable and transient. Particularly low is the immunity developed against falciparum malaria, a higher degree is attained after vivax, and the most stable immunity follows quartan malaria infections. Interesting observations were made in this connection by Schvets in Central Africa (1956). This researcher examined the inhabitants of a number of villages and discovered that absolutely all their children contracted all the forms of malaria during the first years of life. The vivax parasites disappeared from their blood by the time they were approximately 9 years old, by 14 the quartan infection disappeared, and only at a more advanced age was a certain degree of immunity against falciparum malaria created (individuals older than 16 years were only mildly affected by falciparum malaria).

### PROGNOSIS

According to its general features malaria is not a severe disease. Its mortality rate is low with timely diagnosis and early therapy — only 0.2-0.3 per cent. The prognosis is greatly affected by the force and character of the epidemic, the form of the disease, peculiarities of the plasmodial strain, management of therapy, and also the status of the infected population. The starving population of tropical colonies, weakened by strenuous labour, the needy, undernourished immigrants, military troops weakened by long marches and unaccustomed to the climate (during colonial wars) all demonstrated a high malaria mortality rate (up to 30 per cent).

As regards prognosis for recovery we must stress the crucial fact that malaria is absolutely curable. It goes without saying that this concerns cases where treatment is adequate and is instituted at a relatively early period when no irreversible pathologic processes have had time to develop in the organs and systems.

Indications of cure are: cessation of paroxysms, recovery of normal healthy disposition, normal blood count and ESR, return of spleen and



liver to normal dimensions. In some individuals malaria leaves a slightly indurated spleen and slightly enlarged liver; occasionally insignificant vegetative disorders are observed. However, these people are for all practical purposes considered as having recovered from malaria.

### LABORATORY DIAGNOSIS IN MALARIA AND ITS IMPORTANCE

The *thick smear* method is widely known; this is a valuable method of parasitologic diagnosis of malaria. However, certain skill is required in the application of this method, in order to obtain reliable results. If the smear is properly prepared, lixiviated and stained the picture will be clear.

Some medical practitioners still consider that blood tests in malaria infections frequently yield no positive results and that often diagnosis (and treatment!) should be based on clinical data and the notorious "blood formula" (differential white blood count) in which the decisive factors are monocytosis and lymphocytosis that, incidentally, are encountered in numerous other diseases. Such attitudes must be refuted as corrupt and unscientific. They invariably lead to erroneous conclusions.

Y. M. Tareyev (1943) holds that it is absolutely impossible for the plasmodia to be undemonstrable in the peripheral blood during febrile periods. V. S. Nesterov (1955) reports that he did not encounter a single case of authentic malaria when the parasites were not demonstrated. The present authors also consider that in fresh cases demonstration of the plasmodia is always feasible. The cardinal point is the time devoted to examination of the thick smears, as well as the skill of the investigator.

V. S. Nesterov (1955) in his monograph *Diagnosis of Malaria* writes: "Our clinical material shows that the absence of parasites in the blood of patients exhibiting typical pyrexial attacks are explainable by only two causes: either the patient has no malaria, or the search for parasites in his blood was inadequate."

It is fallacious to think, as some medical practitioners do, that the administration of antimalaria preparations excludes the possibility of finding plasmodia in the patient's blood. The parasites are demonstrable in thick smears for 3-4 days after the institution of therapy, as well as in the afebrile periods.

The *erythrocyte sedimentation rate* (ESR) is always accelerated in malaria, particularly in heavy infections.

The gradual fall of the ESR points to clinical recovery or to a decrease in the activity of the malaria infection.

*Serological tests in malaria.* The Wassermann test (with the syphilis antigen) is occasionally positive in malaria, mostly in the acute period and less frequently in protracted cases. However, this test is only weakly positive in the majority of cases (+ and ++); a more intensive reaction is almost never encountered. The weakly positive Wassermann test in malaria is accompanied by negative or very weakly expressed positive sedimentation reactions.

Certain authors have employed the complement-fixation test with an antigen obtained from blood containing great numbers of plasmodia.

*The melano-flocculation test and other reactions.* It has been established that Henry's test is positive in pyrexial, acute forms of malaria (both during paroxysms and in the periods between attacks) but the fresher the infection, the lower is the percentage of positive reactions. However, according to personal data, the reaction to this test in the afebrile period is positive in 50-80 per cent of cases; it gradually decreases with the passage of time from previous attacks. The Henry's test is positive in 20 per cent of healthy people, and even oftener in such diseases as typhoid, cirrhosis of the liver, etc. Consequently, Henry's melano-flocculation test is sooner of negative than positive significance in the diagnosis of malaria: multiple negative responses to this test permit the physician to exclude malaria from the diagnosis. The practical value of the test is not great, therefore the view held by Henry that his test was specific for malaria is at present not shared by any other author. Latest data seem to point to the globulin-euglobulin nature of Henry's test. Other protein-precipitation reactions in malaria should also be looked upon from this point of view.

### BASIC PRINCIPLES OF THERAPY

In the treatment of malaria it is important to strive for a rapid cure of the disease; this, on the one hand, conforms to the most salient prophylactic requirements, and on the other—to the ideal of any and all individual therapy: to relieve the patient of a protracted infection that threatens him with unpleasant complications and to completely restore his capacity for work.

*First principle in therapy of malaria: malaria must be treated in early phases: if the patient's life is in danger the physician must institute therapeutic intervention immediately* on the basis of clinico-epidemiologic diagnosis before the parasitologic analysis of the blood has been performed.

*We consider that immediate therapeutic intervention in cases of severe acute malaria in warm climates is positively imperative.* In cases of erroneous diagnosis the antimalaria preparations administered will cause the patient no harm. On the other hand, should the diagnosis be confirmed by demonstration of the plasmodia in thick smears prepared prior to administration of antimalaria preparations, the prescription of specific treatment prevents grave complications or even fatal outcomes of the disease. The links between chemotherapy and immunity are considered in the following aspect.

1. Malaria cures are effected basically by chemotherapeutic agents, but a certain part in this is also played by the mobilisation of the immunity forces of the organism.

2. The second point concerns the interrelations between early and intensive chemotherapy and the gradual development of immunity, namely: perhaps early and intensive chemotherapy is a factor preventing the development of the immunity concomitant with untreated malaria.

The role of immunisation factors in the therapy of malaria should not be considered from purely academic standpoints alone (immunity and parasitology), but from the practical point of view as well.

“Cures” in the immunological sense (if we waited for them without administration of active chemotherapy) would, in the clinical sense, lead to the development of pronounced para- and metamalarial visceral pathology (splenomegaly, Banti’s postmalarial syndrome, stable hyporegenerative anemia due to bone marrow involvement).

There is no need to speak of the cases when vital considerations (particularly during epidemics) do not permit the physician to consider a spontaneous course of malaria, even if this would cause complete immunity against re-infection. Finally, active intervention into the spontaneous course of the malaria process is postulated by epidemiologic features—the goal of freeing the patient (a source of infection) of the parasites as soon as possible. Foreign literature has at various times carried statements against early chemotherapy. In fresh cases of malaria, when there is no danger to life, the patient should be permitted to go through several paroxysms of the disease in order that he develop his own active immunity, and only after that should therapy be instituted (report of B. Nocht to the Malaria Committee of the League of Nations). *This proposal is absolutely unacceptable, first of all because it is difficult in severe cases to judge by the first days of the disease whether the patient’s life is in danger or not, and, secondly, because every malaria patient is a source of infection since the gametocytes are formed in his blood during the very first week of the disease.*

The statements of certain foreign authors are below any criticism from the viewpoint of contemporary scientific knowledge on the joint participation in the therapeutic process of active chemotherapy and the immunological factors of the organism. This must be emphasised in particular, as of late malaria cures by synthetic preparations are effected *rapidly* and *completely* (with no relapses).

As has been demonstrated by Sinton (1937, 1940) on the basis of epidemiologic data and experiments with monkeys infected with *P. knowlesi*, and by Lourie (1934) in experiments with 10-month avian malaria, chemotherapy is entirely effective both in preventing attacks and in the immunological aspect: the prolonged action of the antigen, be it even in small doses, provides for sufficient immunity; protracted chemoprophylaxis may be accompanied by the development of a concomitant residual immunity. Immunity develops notwithstanding transient chemoprophylactic measures and the short contact of the organism with the antigen.

R. Bastianelli (1936), basing himself on a study of the materials of the League of Nations Malaria Committee concluded that no difference was generally observed (in the development of immunity—I. K.) between untreated cases and cases where the disease was treated from the very first attack. Lourie, experimenting with canaries infected with *P. cathe-merium*, prescribed non-toxic doses of quinine in order to curtail the initial attack. He succeeded in establishing that the birds cured of malaria responded to superinfections in the same manner as did non-treated birds.

Correctly instituted chemotherapy does not prevent the development of immunity.

M. F. Boyd (1940) observed the course of artificially acquired tertian malaria (sporozoite infection); he established that the percentage of relapses (60) was not lower in cases when therapy was commenced at late stages of the disease than when early therapy was instituted.

The treatment of malaria, particularly in severe cases, must follow a certain system. Even in ideal cases of chemotherapy, when rapid and highly efficient combined treatment of malaria are instituted, *systematic treatment is indispensable*.

The principle of malaria therapy lies in the prescription of doses of antimalaria preparations sufficient for the production of the therapeutic effect. This point is based on contemporary knowledge of the direct mechanism of the action of antimalaria preparations.

*Resistance to antimalaria preparations.* The question of dosage is closely connected with the extremely important question of so-called resistance to chemical preparations. The latter, as we know, develops more frequently as a result of irrational, non-systematic therapy with insufficient doses of chemical preparations.

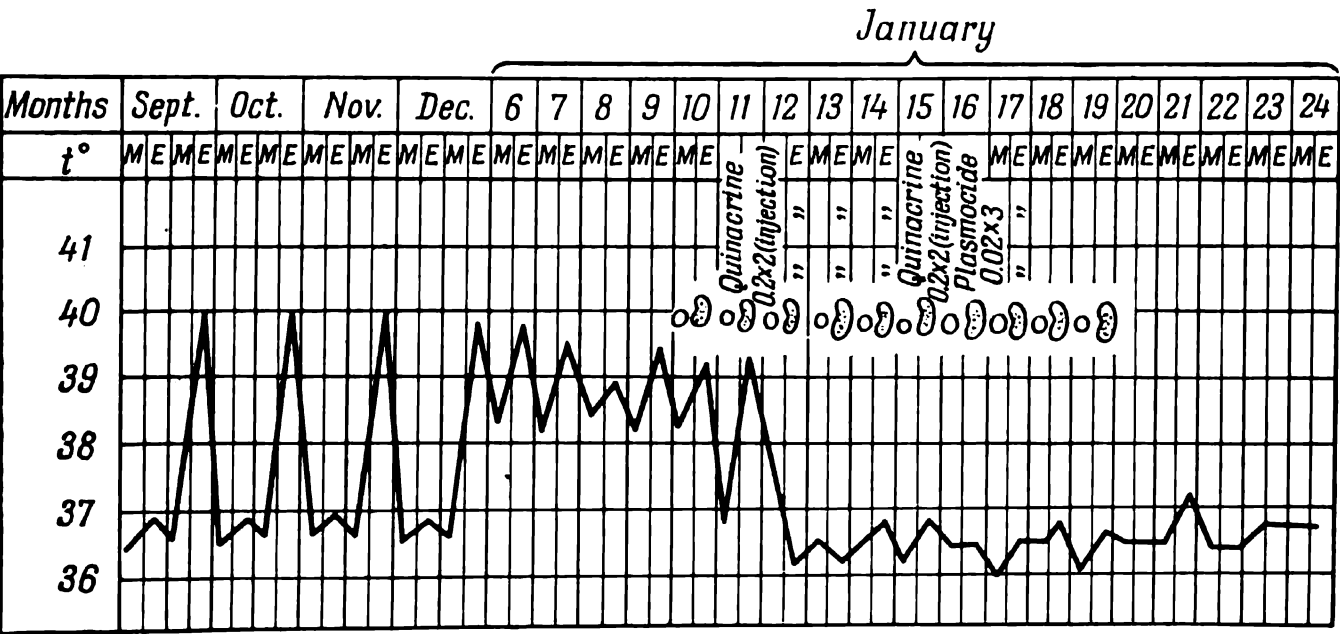


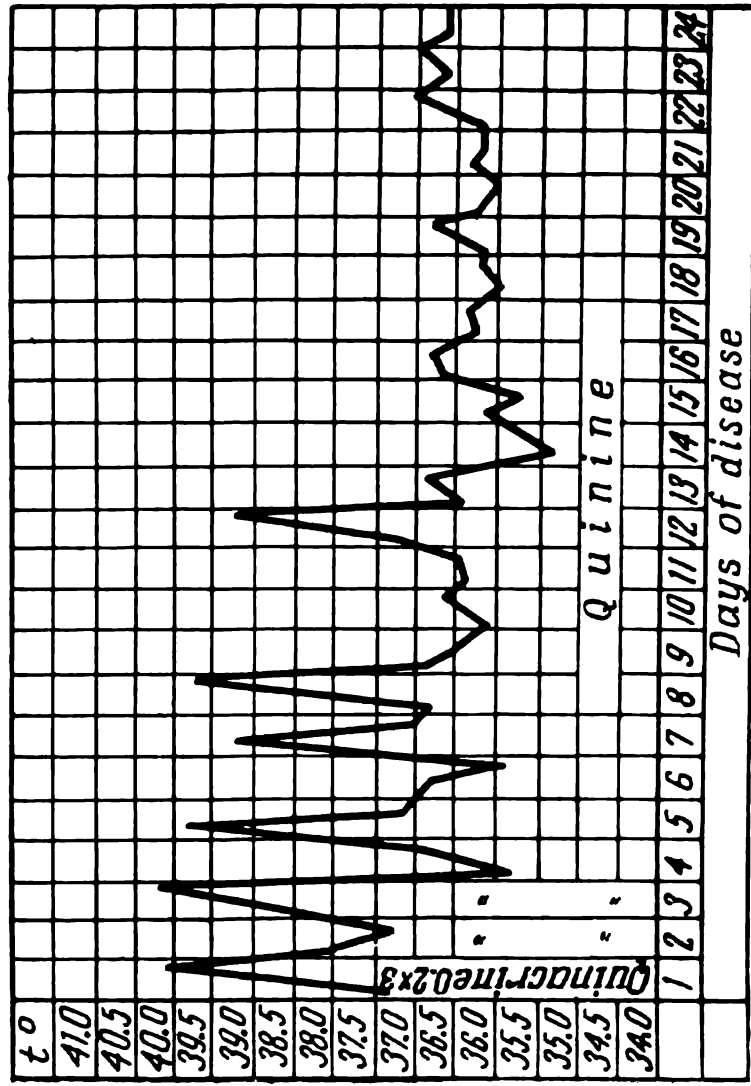
Fig. 22. Protracted falciparum malaria curtailed by enlarged doses of quinacrine

The authors have had occasion to observe several quinacrine-resistant (acrichin-resistant) cases (naturally, we look upon this quinacrine-resistance as only relative). Cases of resistance to quinine, bigumal (paludrine), chloridin (pyrimethamine) are also encountered (Figs 22, 23, 24).

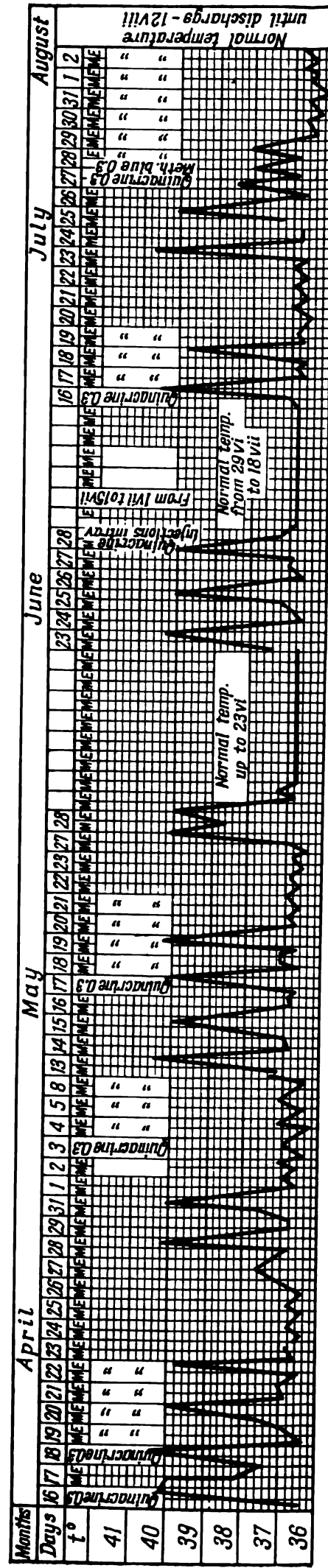
Consequently, the points dwelt upon above concerning the direct parasitocidal action of chemopreparations and on the resistance of the malaria plasmodia show that undeniable positive effects can be attained only with sufficient doses of antimalaria preparations.

The principle of individualisation must unquestionably be the basis of the entire system and tactics of malaria treatment. In each separate case

**Fig. 23. Alternative administration of quinacrine and quinine in a rare case of quinacrine-resistant tertian malaria (0.6 g for 3 consecutive days ineffective). Addition of quinine resulted in complete curtailment**



**Fig. 24. Quinacrine-resistance in tertian malaria**



the physician, basing himself on the severity, clinical form and tenacity of the disease, uses his own discretion in varying the methods he employs (a certain increase in the initial doses in severe cases, "zigzag" increases of doses in cases of resistance to ordinary doses, administration of injections, combination of various preparations, their alternation, etc.).

### ANTIMALARIA PREPARATIONS

The principal medicines employed in the specific treatment of malaria are chloroquine, amodiaquin, acrichin (quinacrine, mepacrine, atabrine), bigumal (paludrine), chloridin (pyrimethamine), plasmocide, quinocide, primaquine, quinine (by special prescription).

The preparations most efficacious in arresting attacks of malaria are the derivatives of 4-aminoquinoline — chloroquine and amodiaquin.

*Chloroquine diphosphate* (aralen, avlochlor, chimanin, delagol, gontochin, resochin, sanochin) is 7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline diphosphate. It is a white, crystalline powder with a bitter taste, freely soluble in water. Aqueous solutions are stable and do not change upon being heated to 100 °C.

*Chloroquine sulfate* (nivachin B) is available in tablets containing 0.136 g of the substance (0.1 g of base), 0.204 g (0.15 g of base), and 0.408 g (0.3 g of base).

*Most important therapeutic properties of chloroquine.* Chloroquine possesses a high therapeutic activity against all forms of malaria, rapidly curtails its attacks owing to its marked schizontocidal properties. It does not affect either the exoerythrocytic forms of malaria parasites or the *P. falciparum* gametocytes. Owing to a rapid suppression of the formation of young forms of plasmodia of all species chloroquine restricts the formation of gametocytes of the tertian and quartan forms of malaria; cessation of the production of *P. falciparum* gametocytes occurs much later. Chloroquine possesses low toxicity and is well tolerated by infants and pregnant women.

*Side effects of chloroquine.* Protracted individual prophylactic courses of chloroquine cause in some people headache, pruritus, gastrointestinal disorders, accommodation disturbances. These symptoms are not very marked and clear up rapidly after cessation of chloroquine administration. Rapid intravenous installation of chloroquine solutions may bring on collapse.

*Contraindications for chloroquine* are practically non-existent.

*Amodiaquin* (camoquin, flavoquine, miaquin) is the generic name for the antimalaria drug 4-(7-chloro-4-quinolylamino)-alpha-diethylamino-0-cresol. The therapeutic and pharmacologic properties of this substance are close to those of chloroquine. It is supplied in tablets containing 0.2 g of the basic substance.

*Acrichin* (Soviet preparation) (synonyms: atabrine, atebtrin, chemiochin, chinacrine, haffkinine, italchina, malaricida, mecaforine, mepacrine, methochin, methoquine, palacrin, palusan, pentilen, quinacrine, penicridine

and others) is a synthetic preparation based on an acridine nucleus; it is a dehydrochloride of 2-methoxy-6-chloro-9-beta-diethylamino-alpha-methylaminoacridine. (The British name for acrichin is mepacrine hydrochloride, the American — quinacrine hydrochloride.) It occurs as a fine crystalline powder of a bright yellow colour, very bitter. Dissolves in water at room temperature in concentrations of 3 g per 100 ml, in warm water — 4-5 g per 100 ml.

Acrichin is available in the following forms: 1) yellow 0.1 g tablets (for adults) or 0.5 g tablets or sugar-coated pills for children; 2) green tablets (stained with methylene blue) containing 0.1 g of acrichin and 0.02 g of plasmocide per tablet (for adults), or 0.1 g of acrichin and 0.01 g of plasmocide (tablets or sugar-coated pills for children); 3) pulverised for preparing solutions for injection.

A 4 per cent solution of acrichin is employed for injections. Should such a solution evoke infiltrations the concentration may be lowered (2-3 per cent), but larger amounts must then be administered. Upon cooling 4 per cent solutions the substance is partially precipitated; however, slight warming dissolves the precipitate. Acrichin is injected intramuscularly. In rare cases (malignant forms of malaria) a 4 per cent solution is introduced intravenously in doses of 2.5 ml (0.1 g of acrichin) (instillation must be very slow to avoid collapse).

*Most salient therapeutic properties of acrichin.* Acrichin is a schizontotropic substance. Its effect on gametocytes is negligible and is displayed only in tertian and quartan forms of the disease. It has no effect on the gametocytes of *P. falciparum*.

Acrichin arrests the chills and fever within 3-5 days (on the average 86-91 hours) after institution of therapy in all forms of malaria; however, complete disappearance of the schizonts from the peripheral blood occurs only after 100-108 hours have passed (Fig. 25).

Acrichin appears in the blood soon after administration per os, and still sooner after intramuscular injections; it is slowly excreted by the kidneys (in the majority of cases within the first two weeks, but sometimes in 5 weeks); the substance is partially decomposed in the body.

The preparation is well tolerated and possesses a low toxicity. Dyspeptic symptoms (nausea, vomiting) are observed chiefly in instances of individual intolerance or during periods of high temperature. These symptoms are of short duration.

*Side effects of acrichin.* The commonly known side effects of acrichin (quinacrine) are the protracted yellowish tinge acquired by the skin (the sclera does not turn yellow). In some cases this tinge may be retained for 2-3 months (its intensity decreases gradually). Acrichin "jaundice" is absolutely harmless and is not associated with any liver trouble.

The most characteristic side effects of acrichin are nervous and mental disorders. Usually such disorders are due to overdosage or poor excretion of the preparation. They are represented, mainly by mild symptoms of excitation of the motor and speech centres, dizziness, acrichin drunkenness, insomnia, trouble with memory and concentration, general depression.

Acrichin intoxication is occasionally accompanied by Romberg's sign, tremor of the fingers, in rare cases — by nystagmus. The authors have observed a number of transient disorders in a child manifested by motor excitation, diplopia, and strabismus.

There are a number of acrichin psychoses which are observed very rarely, chiefly in cases of overdosage, expressed in 1) maniacal excitation with a mental disorder of the amentive type; 2) a schizophrenic-like reaction with various degrees of mental disturbance of the amentive type;

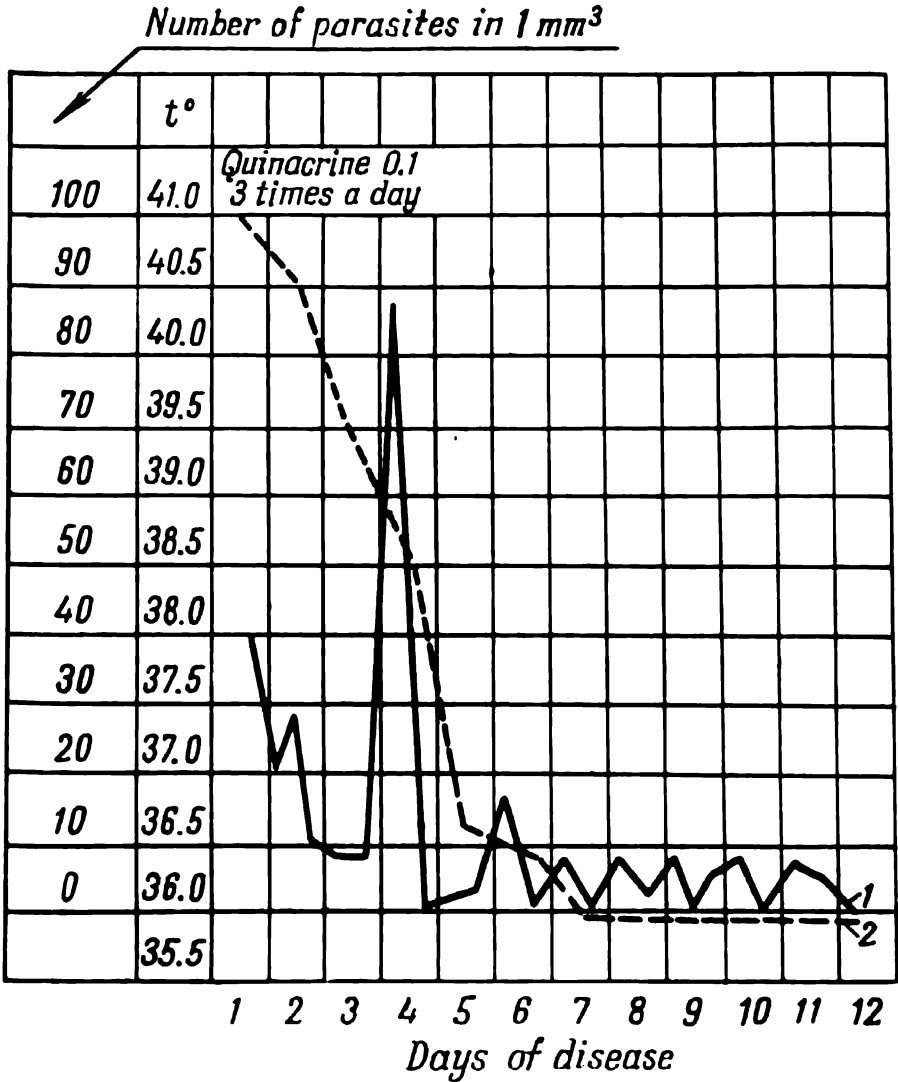


Fig. 25. Reduction of temperature and dynamics of disappearance of plasmodia from peripheral blood in malaria treated with acrichin (quinacrine)

1 — temperature; 2 — number of parasites

3) an amentive-delirious form with hallucinations of hearing and epileptiform excitation. Acrichin (quinacrine) psychoses are mostly observed in patients with unstable mentalities. The duration of these disorders are short, no more than a week or two.

The percentage of neuropsychic complications of acrichin therapy is low (tenths of a per cent).

Acrichin therapy is discontinued upon the appearance of the above complications. It is advisable to prescribe bromides, chloral hydrate, and,



for accelerating the elimination of the preparation from the body, glucose infusions, sodium citrate per os, fluids in excess.

*Acrichin (quinacrine)* is contraindicated in mental disorders and when the preparation is known to have evoked neuropsychic disorders in the past. It is relatively contraindicated for individuals with labile neuropsychic spheres, as well as in cases of renal dysfunction, high bilirubin levels in the blood associated with liver deficiency and retention of acrichin in the body (failure of evacuation with the urine).

*Bigumal (paludrine)*. In 1944, a valuable new antimalaria preparation was synthesised by Rous, Kerd, and Davy.

These researchers set themselves the task of evolving a preparation that would effect not only the schizont phases of the plasmodia, but also the exoerythrocytic (tissue) phases. By this they hoped to suppress the paroxysms of the disease and to prevent relapses, as the latter are associated with the tissue phases of the parasites.

The synthesis of paludrine was something new in the chemotherapy of malaria, for this preparation was no quinoline derivative.

An analogue of paludrine was synthesised in the Soviet Union under the name of bigumal by A. F. Bekhli, V. N. Ufimtsev, et al. in 1947.

Chemically bigumal is  $N_1$ -(para-chlorophenyl)- $N_5$ -isopropylbiguanide hydrochloride. It is a fine white crystalline powder with a bitter taste. Bigumal hydrochloride dissolves in water at 20°C in concentrations of 1g/100 ml.

*Basic therapeutic properties of bigumal:*

- 1) it affects the schizont stages of the parasites, but is most effective for *P. falciparum*;
- 2) it affects the primary (pre-erythrocyte) tissue forms of the parasites (Fig. 26, a, b, c).

The preparation is available in the following forms:

- 1) white tablets, containing 0.1 g bigumal per tablet (for adults) or 0.05 g (for children);
- 2) grey tablets containing 0.1 g bigumal and 0.02 g plasmocide (for adults) or 0.05 g bigumal and 0.01 g plasmocide (for children);
- 3) a powder for preparing 1 per cent solutions for intravenous injections (in comatose malaria).

After ingestion bigumal rapidly appears in the blood and is detected in the urine one hour after ingestion. It is eliminated by the kidneys quicker than quinacrine (acrichin) — within one week after termination of treatment.

The toxicity of bigumal is low; it is well tolerated by patients, including pregnant women and children.

The dyspeptic symptoms occasionally observed after administration of bigumal (nausea, vomiting) are due rather to the malarial attack than to the preparation as its administration in apyrexial periods is not accompanied by such symptoms.

A leukemoid (granulocytic and monocytic) reaction may occasionally be observed in the blood during bigumal therapy: leukocytosis may rise to 10,000-15,000, the neutrophil values shifting to metamyelocytes and

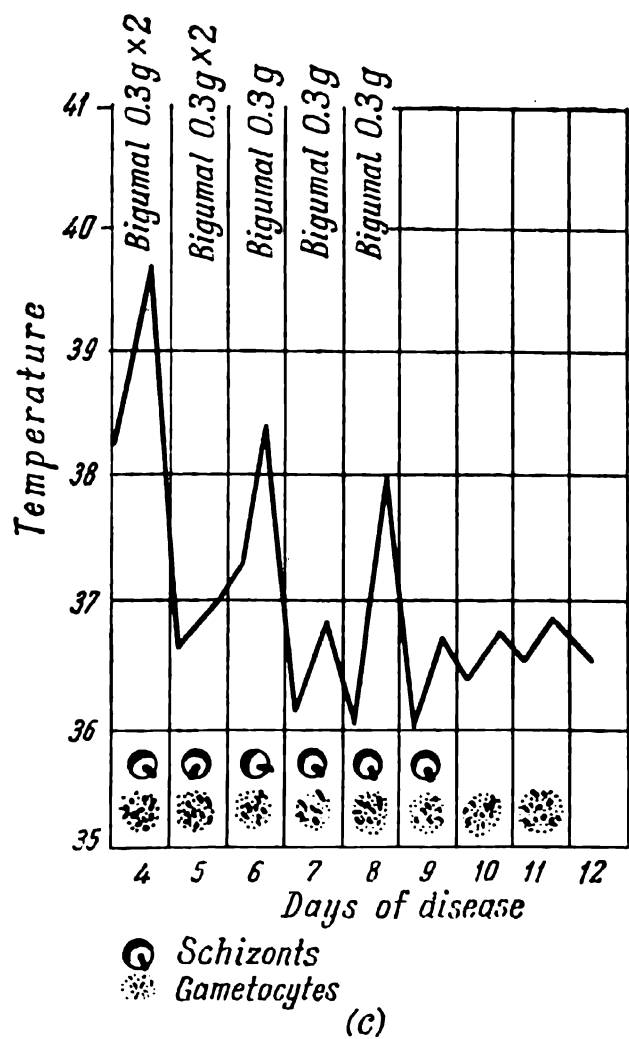
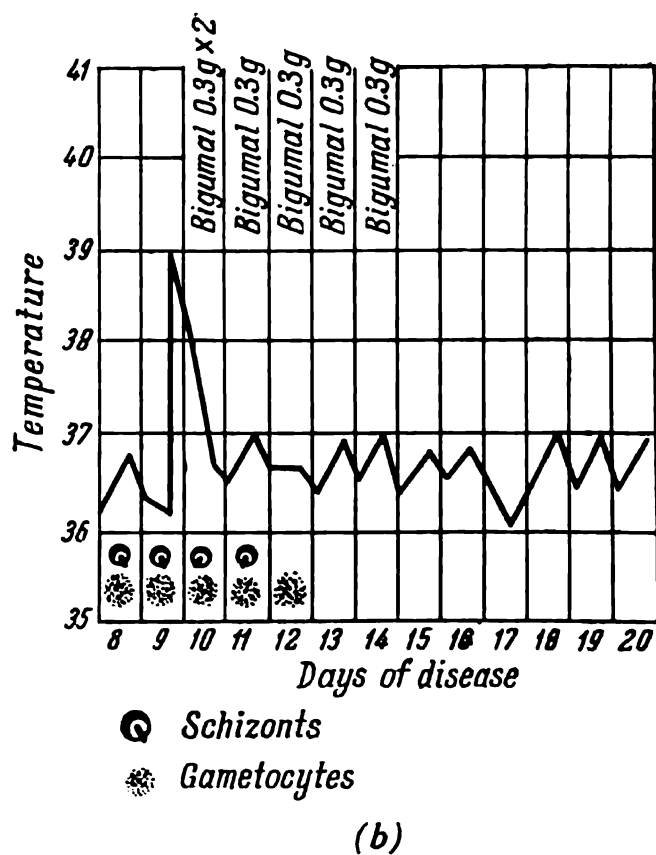
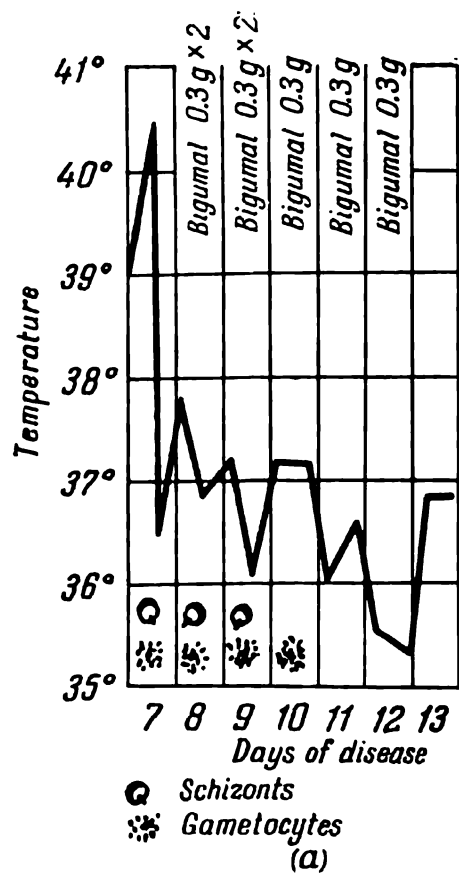


Fig. 26. *a, b, c.* Febrility dynamics and disappearance of parasites from peripheral blood in cases of tertian malaria treated with bigumal (paludrine)

myelocytes; reports have been published on the increase of the white blood count to 30,000-50,000 in protracted administration of large doses of bigumal.

*Chloridin* (daraprim, malocide, pyrimethamine) is the name used in the Soviet Union for 2,4-diamino-5-para-chlorophenyl-6-ethylpyrimidine; it is a white crystalline powder without odour or taste.

*Therapeutic properties of chloridin.* The preparation is active against the schizonts of all species of malaria parasites; however, it is less efficient than the 4-quinolylamino derivatives (chloroquine, amodiaquin), therefore its suppressive effect on malaria attacks is relatively slow. The preparation affects the sexual forms of the parasites, rendering them incapable of development in the mosquito. It is active against the primary exoerythrocytic forms.

In certain areas an acquired stable resistance of the malaria parasites against chloridin has been observed.

The toxicity of chloridin administered in ordinary doses is very slight.

*Side effects of chloridin.* Prolonged administration of the preparation in daily doses of 0.025 g may bring on the development of anemia.

*Chloridin is contraindicated* in diseases of the hematopoietic organs.

*Plasmocide* is a synthetic Soviet preparation, its effect is analogous to that of the pamaquine or plasmochin produced in other countries. It is the methylene bis-salicylate of 6-methoxy-8-diethylamino-propylamino-quinoline; it occurs as an orange-yellow odourless, slightly bitter crystalline powder, insoluble in water.

The preparation is supplied in tablets in combination with acrichin or bigumal (see above).

The maximum permissible daily dose of plasmocide for adults is 0.06 g, i.e., 3 tablets of a combination of this preparation with acrichin or bigumal. Children are given correspondingly lower doses (see below).

In no case whatsoever is the indicated daily dose of plasmocide to be exceeded, owing to its toxicity.

*Basic therapeutic properties of plasmocide.* The action of plasmocide is directed principally against the sexual forms of the plasmodia, particularly against the *P. falciparum* gametocytes. Its importance in the treatment and prevention of malaria can therefore not be overemphasised. Within 1-2 days after the administration of even small doses of plasmocide the gametocytes become incapable of infesting the mosquito, and within 4-5 days disappear from the blood altogether.

Plasmocide also affects the tissue forms of the plasmodia; therefore its administration in combination with schizontotropic agents lowers the possibility of relapses.

*Side effects of plasmocide.* Excessive ingestion of plasmocide induces intoxication displayed by headache, substernal pain, paresthesia and trigeminal neuralgia. Excessive overdoses cause syndromes of the ataxic, polyneuritic, amaurotic and encephalitic types.

The most frequently observed symptom of plasmocidal intoxication is an acute syndrome of Leyden-Westphal ataxia. Systemic ataxia of this type evokes a peculiar sensation of constriction in the face, rarer in other

parts of the body; as a rule this sensation is followed by lesions of the optic nerves. Usually these nervous symptoms appear acutely after administration of plasmocide. In addition to lesions of the optic and trigeminal nerves dysfunction of other cranial nerves also appear, as, for instance, of the facial and vagus nerves (nasal sounds in speech, deglutitory disturbance). Of the other symptoms observed in patients pronounced nerve root symptoms are important (rigidity of the neck, hyperesthetic zones, sensations of constriction, pains). Slight impairments of peripheral sensitivity are observed rarely.

Of the severe complications following plasmocide administration the authors have observed amaurosis, plasmocidal encephalitis accompanied by significant vegetative disorders in a female patient after a month of almost uninterrupted plasmocide therapy, and also hemoglobinuric fever. It is positively clear that the greater part of complications is associated with overdosage and prolonged administration of this preparation without the interruptions necessary in this treatment. Thus, in a case of optic nerve atrophy observed in our clinic the patient had taken 12 plasmocide tablets within 24 hours (to provoke an abortion).

According to the data of Y. M. Tareyev (1943), overdosage of plasmocide has been established to be the leading cause of complications in 68 per cent of cases (in 56 per cent excessive overdosage, in 12 per cent — relative overdosage of therapeutic norms); overdosage was noted in 82 per cent of cases of optic nerve atrophy. With normal doses plasmocide is not dangerous, although it does occasionally induce side effects.

The rapidity with which the intoxication appears is connected with the extent of overdosage. Thus, in several cases of ingestion of large quantities of plasmocide (to commit suicide or provoke an abortion) impairment of vision was observed within 4-5 hours after ingestion of the drug.

The individual reaction of the patient is also an important factor. Plasmocide intoxication occurs more frequently in children than in adults.

*Contraindications for plasmocide are:*

- 1) diseases of the fundus oculi and the optic nerve;
- 2) encephalitis or meningo-encephalitis in the present or the past;
- 3) toxic symptoms evoked in the past during plasmocide therapy;
- 4) age less than one year.

*Treatment of nervous system complications.* Upon the first signs of plasmocide intoxication its administration should immediately be discontinued, stomach lavage performed and excessive fluid intake and alkaline drinks prescribed. Other recommendations: caffeine injections, retrobulbar injection of 0.1 per cent atropine (0.2-0.5 ml), injection of vitamin B<sub>1</sub> (0.5-1 ml of a 5 per cent solution), vitamin B<sub>12</sub> in 100-200 µg doses, administration of 0.02 g of nicotinic acid three times a day. Narcotics and somnifacient drugs are not advisable.

*Quinocide* is a relatively new antimalarial preparation synthesised in 1952 by V. I. Stavrovsky and M. B. Braude in the Central Institute of Malaria, Medical Parasitology and Helminthology in Moscow. (Its action is analogous to that of primaquine).

Quinocide is 6-methoxy-8-(4-aminopentyl)-aminoquinoline hydrochloride. It occurs as a light-orange fine crystalline powder with a moderately bitter taste; it is unstable in moist atmospheres, soluble up to 50 per cent in water at room temperature.

Quinocide is supplied in sugar-coated pills containing 0.005 or 0.01 g of the preparation.

Quinocide tablets must be kept in dark glass containers with ground glass stoppers or good corks, in a dry place. Marked colour changes (intensive green or black) signify that the tablets have decomposed and should be destroyed.

Extensive clinical tests of this preparation were carried out by P. G. Sergiyev (1956), A. Y. Lysenko and N. N. Ozeretskoy (1955), A. A. Gontayeva et al. (1955). Practical experience attained in the treatment of over 10,000 patients in different zones of the Soviet Union has shown that quinocide ensures stable cures (with no relapses) of tertian malaria in 97 per cent of cases.

*Basic therapeutic properties of quinocide.* Quinocide is effective against the exoerythrocytic forms of *P. vivax*; owing to this it prevents early and late relapses of tertian malaria in the majority of cases with short periods of incubation, and early relapses of this disease in cases of prolonged incubation. It is also active against the sexual forms of the plasmodia. Quinocide treatment is indicated for preventing relapses, and also as a pre-epidemic prophylactic measure against vivax malaria. The activity of quinocide against the erythrocytic forms of the parasite is insufficient, therefore it is not employed for suppressing malarial paroxysms.

*Primaquine* is 8-(4-amino-1-methylbutylamino-6-methoxy-quinoline); it is supplied as primaquine diphosphate in tablets, each of which contains 0.0075 g of the basic substance.

*Therapeutic properties of primaquine.* In ordinary doses the preparation does not affect the schizonts, but is very active against the gametocytes of all species of plasmodia and their exoerythrocytic forms.

*Side effects of primaquine.* Overdosages cause anorexia, nausea, cyanosis, abdominal pains, melanuria, vomiting, pains in the chest, weakness, leukopenia, anemia, methemoglobinemia, hemolysis. The latter condition appears in susceptible individuals the number of whom is very low in temperate zones, but may attain 10 per cent in certain warm countries.

All these symptoms clear up after the administration of the preparation is discontinued.

*Contraindications for primaquine therapy.* It is not advisable to prescribe primaquine together with acrichin or soon after it.

*Quinine* is a natural alkaloid obtained from cinchona bark. The base of its chemical structure is the quinoline structural unit. Chemically quinine is methoxyquinoline-vinyl-carbonyl.

Quinine is employed in the form of the following salts:

1) quinine hydrochloride (*Chininum hydrochloricum* or *quininae hydrochloridum*); white, silky, glistening needle-like crystals with an ex-

tremely bitter taste; contains approximately 82 per cent of basic quinine; is soluble in 30 parts of cold water and one part of boiling water;

2) quinine dichloride (Chininum bimuriaticum or quininae dihydrochloridum); white bitter crystals containing approximately 73 per cent of basic quinine, is soluble in 0.7 parts of water;

3) quinine sulfate (Chininum sulfuricum or quininae sulfas); fine, white, needle-like crystals, very bitter; contains more than 72 per cent of basic quinine; is soluble in 800 parts of cold and 25 parts of boiling water.

Quinine hydrochloride and quinine sulfate are administered per os in powders, tablets, wafers and capsules. Administration of tablets that have been kept for long periods of time is permissible after their solubility in water has been tested; if solubility is poor the tablets should be crushed before ingestion.

Injections are best given with quinine dichloride. Ampouled solutions of this substance are available (25 and 50 per cent solutions). If the injection of the 50 per cent solution causes infiltration it should be replaced by the 25 per cent solution.

Another prescription of quinine solution may also be recommended for injections (with antipyrine):

Rp. Chinini hydrochlorici 6.0  
Antipyrini 4.0  
Aq. destill. 12.0  
Sterilis!  
DS. For injections

For intravenous injections a 5 per cent solution is best:

Rp. Sol. Chinini hydrochlorici 5% 30.0  
Sterilis!  
DS. For intravenous injections

*Basic therapeutic properties of quinine.* Quinine possesses a schizontotropic action. In the treatment of acute attacks of malaria with quinine the schizonts usually disappear from the blood within 4 days. Quinine is rapidly absorbed into the blood when taken orally (in approximately 4-6 hours), and is generally evacuated within two days.

*Side effects of quinine* are most commonly caused by excessive doses; however, individual susceptibility is also important.

Basic symptoms: noise and ringing in the head, headache, dizziness, temporary impairment of vision (vascular type of toxic spasm). Tolerance toward quinine is heightened by combining it with caffeine, calcium bromide and aspirin.

Large overdoses (3-4 g) of quinine have a *toxic effect*. The symptoms are acute headache, noise in the head, and in certain cases a stable deafness, loss of the sense of taste and smell, photophobia, later — blindness and mental depression.

It is recommended to treat all the indicated complications, amaurosis in particular, with caffeine and papaverine, and, in cases of collapse, with stimulants.

The principal symptom of idiosyncratic reaction to quinine is the appearance of toxic phenomena following the administration of small doses of the preparation. Idiosyncrasy has been observed following doses of 0.05-0.1 g. The symptoms are: tremor of the hands, palpitations with tachycardia, panting breath, dizziness, pruritus, and urticaria. Discrete cases of death following ingestion of quinine have been described.

Severe idiosyncrasies (allergies) to quinine include quinine hemoglobinuria, acute agranulocytosis, thrombocytopenic purpura, etc. In such cases the allergic reaction is treated with ephedrine, calcium preparations, adrenalin.

### TREATMENT SCHEMES

Paroxysms of all the forms of malaria are suppressed most rapidly by the derivatives of 4-quinolylamino-chloroquine and amodiaquin.

*Chloroquine therapy* in all forms of malaria is conducted on three consecutive days.

Chloroquine is prescribed per os; the first day two 0.6 g doses of the basic substance are administered, on the second and third days only one 0.3 g dose of the base is given. In severe forms of malaria as much as 0.9 g of the base may be administered in two doses on the first day of treatment (0.6 g first dose and 0.3 g six hours later). In malignant forms of the infection solutions of the preparation are administered parenterally (see lower).

*Amodiaquin* is prescribed for 3 consecutive days; on the first day 0.6 g of the base is administered and 0.4 g on each of the two following days.

In endemic sites of malaria the indigenous population has acquired a relative immunity to this disease, therefore the above preparations may be prescribed to be taken only once (Table 4).

Table 4

Treatment of Malaria Patients with Single Doses of Chloroquine or Amodiaquin (after Covell et al., 1956)

Drugs	Doses in grams for different age groups					
	Adults	Older than 12 yrs	6 to 12 yrs	3 to 6 yrs	1 to 3 yrs	Younger than one yr
Chloroquine base . . . . .	0.6*	0.45-0.6	0.45	0.3	0.225	0.037-0.075
or						
Amodiaquin base . . . . .	0.6	0.4-0.6	0.4	0.3	0.2	0.1-0.15

\* Four 0.25 g resochin tablets or four 0.205 g nivachin B tablets

In order to suppress the gametocytes of *P. falciparum* it is recommended to combine chloroquine and amodiaquin treatment with the administration of primaquine for three days in 0.015 g daily doses, or plasmo-cide (0.06 g per day).

Chloroquine, amodiaquin, and also bigumal (see lower) are agents that provide radical cures in the majority of *P. falciparum* cases; radical cures of patients with tertian, quartan and ovale infections require a combination of these preparations with quinocide and primaquine (see lower).

*Acrichin* (quinacrine) is prescribed on 4 or 5 consecutive days alone or in combination with plasmocide. Four-day course of treatment: a double dose of acrichin on the first day, adults receiving 0.3 g twice on this day, and 0.3 g per day on the following days in one or two doses. Five-day course: 0.3 g of acrichin daily.

In both the four- and five-day courses no more than 0.06 g of plasmocide is given daily, in one or two portions (for adults). Children younger than four years old are given acrichin per os in 0.5 per cent solutions prepared with acrichin powder or tablets (five 0.1 g tablets are dissolved in 100 ml of water). A teaspoonful of an 0.5 per cent solution contains 0.025 g of acrichin.

Children may also take acrichin in the form of sugar-coated pills, and also with jam or some other sweet substance after the pills or tablets have been thoroughly crushed. In severe cases of malaria acrichin treatment should be commenced with intramuscular injections of solutions of this preparation; such injections are well tolerated even by infants. After the paroxysms have been suppressed treatment is continued by oral administration.

*Bigumal* is prescribed mostly in cases of *P. falciparum* infections, alone or in combination with plasmocide, for five consecutive days. A double dose (0.6 g) is given the first day (0.3 g twice), on the following four days 0.3 g are given per day in one or two doses. In severe cases the administration of bigumal may be prolonged for another two days (7 days in all).

Table 5

Acrichin, Bigumal, and Plasmocide Dosage for the Different Age Groups

Age groups	Daily dose of acrichin or bigumal per os in g	Daily dose of 4 per cent acrichin solution for intramuscular injection in ml	Daily dose of plasmocide in g
Up to 1 yr ..	0.025	0.5-1.0	Not prescribed
1-2 yrs .....	0.05	1.0-1.25	0.01
2-4 yrs .....	0.075	1.5-2.0	0.015
4-6 yrs .....	0.1	2.0-3.0	0.02
6-8 yrs .....	0.15	3.0-4.0	0.03
8-12 yrs ....	0.15-0.2	4.0-5.0	0.03-0.04
12-16 yrs ...	0.25	5.0-6.0	0.05
Over 16 yrs .	0.3	6.0-7.5	0.06



The daily dose of plasmocide must not exceed 0.06 g; it is prescribed for no longer than 5 days.

*Chloridin* is not employed for the treatment of acute attacks of malaria, as its suppressive action is relatively slow. It should be prescribed in combination with chloroquine or acrichin.

Daily doses of chloridin: 0.03 g for adults; for children younger than one year — 0.0025 g; from 1 to 2 years — 0.005 g; from 2 to 4 years — 0.0075 g; 4-6 years — 0.01 g; 6-8 years — 0.015 g; 8-10 years — 0.02 g; 11-16 years — 0.025 g. A double dose is administered on the first day of treatment.

Therapy may be conducted with darachlor tablets. Each tablet of this drug contains 0.15 g of chloroquine base and 0.015 g of chloridin (daraprim). Patients possessing no immunity against malaria receive 4 tablets of darachlor on the first day of treatment and 2 tablets a day on the second and third days. In endemic sites the local population possesses some immunity against malaria and treatment is therefore restricted to the administration of only 4 tablets of darachlor.

*Quinine* is used in the absence of the above-listed preparations. Usually 1.0-1.2 g of quinine sulfate is prescribed per os for 5-7 days. In severe cases of tertian and quartan malaria and in *P. falciparum* infections 1.5 g of quinine hydrochloride (or 2.0 g of quinine sulfate) is prescribed daily (in 2-3 doses), or upon clinical indications 0.5 to 1.0 g of quinine dichloride is injected twice a day into the deep-lying subcutaneous tissue.

Quinine doses for children are prescribed according to the following calculation: up to one year 0.01 g per month of life, but no more than 0.1 g; from one to ten years 0.1 g per year of life; from 10 to 15 years 1.0 g daily; after 15 years the adult dose is administered. Generally speaking, quinine is rarely employed for malaria therapy at present.

*Euquinine* — quinine ethylcarbonate — is a fine, white, almost tasteless powder. It is prescribed in doses  $1\frac{1}{2}$  times greater than quinine doses; in heavy infections the activity of this preparation is insufficient.

Malaria occurring during pregnancy should be treated with particular care owing to the unfavourable effect of malaria on the pregnancy and on the development of the fetus, and also to the severe course malaria takes in pregnant women. Treatment is conducted in the usual manner with the usual preparations.

Antimalaria preparations are well tolerated by pregnant women. Particular care is necessary only with quinine: its daily dose must not exceed 1.0 g and should be divided into 4-5 portions to avoid miscarriage. Acrichin, chloroquine, and amodiaquin have no unfavourable effect on the uterus or the fetus.

*Radical cures* of tertian, quartan and ovale malaria are attained by a combination of preparations suppressing attacks with drugs active against the exoerythrocytic forms of the parasites.

*Quinocide*. In the acute stage of the malaria infection the paroxysms are arrested by chloroquine or amodiaquin, or, in their absence, by acrichin (quinacrine). Quinocide is prescribed directly following termination of the course of these preparations.

Quinocide therapy is managed by one of the two following plans:

Plan 1: 0.03 g of quinocide daily in one or two portions (preferably after meals) for 10 consecutive days.

Plan 2: 0.02 g of quinocide daily for 14 consecutive days.

Table 6

Daily Doses of Quinocide for Different Age Groups (in g)

Plan	Age groups in years						
	Up to 1 yr	1-2 yrs	3-4 yrs	5-7 yrs	8-12 yrs	13-15 yrs	16 yrs and older
1	—	0.005	0.0075	0.01	0.015	0.02	0.03
2	0.0015	0.0025	0.005	0.0075	0.01	0.015	0.02

For the prevention of relapses quinocide is also prescribed (without any preliminary administration of schizontotropic preparations) in all cases of attacks of quartan or tertian malaria in the current or previous year if these patients have not taken the preparation previously.

Quinocide may be prescribed as a pre-epidemic prophylactic measure against tertian malaria with a protracted incubation period for individuals who might have been infected with this type of malaria in the previous season.

Quinocide is prescribed no later than one month before the mass appearance of fresh infections in the given locality, for positively all persons who might have been infected (who were in danger of infection during the previous season).

The treatment of parasite carriers is commenced with schizontotropic preparations (chloroquine, amodiaquin, acrichin) and followed with quinocide.

In the doses indicated in Table 6 the toxicity of quinocide is very low. Side effects are rarely observed. They are incurred for the most part by the simultaneous ingestion of quinocide and other antimalaria preparations; another cause may be the weakness of the patient.

The possible side effects are: dyspeptic disorders, cyanosis of the lips and nails, in solitary cases symptoms of kidney and bladder trouble (micro-hematuria, dysuria, slight hemolysis, moderate leukopenia, or, on the contrary, leukocytosis). All these symptoms pass away soon after discontinuation of the preparation.

There are no absolute contraindications for quinocide administration. It is relatively contraindicated by blood system disorders (anemia, leukopenia), diseases of the kidneys, and by coronary cardiosclerosis with symptoms of angina pectoris. Quinocide treatment of weak, severely ill patients should be conducted by plan 2, in hospital conditions.

*Primaquine* is prescribed in doses containing 0.015 g of the basic substance for 14 consecutive days. The paroxysms of malaria must first be suppressed with chloroquine or amodiaquin. Acrichin is not permissible for this purpose.

Indications for primaquine are the same as for quinocide.

### OUT-PATIENT TREATMENT FOR MALARIA PATIENTS

The management of out-patient therapy of malaria patients is very important, and it should be commenced at the medical institution the patient has applied to. Subsequently the physician's orders are carried out by the local trained nurses or special acrichin therapists who visit the patient at home, or by the staff of the medical post at his place of work. The patient must take the drugs in the presence of a nurse.

In schools, children's homes, nursery schools and crèches malaria patients are treated by the medical staff attached to the establishment.

Malaria patients are hospitalised in the acute period (during the epidemic period this is compulsory). Blood tests for malaria are obligatory upon admission to the hospital and when the patient is dismissed.

### TREATMENT OF PERNICIOUS FORMS OF MALARIA

In cases of pernicious malaria (comatose and other forms of cerebral malaria, forms resembling typhoid or sepsis, icteric and hemorrhagic forms), encountered mostly in warm and tropical climates, treatment should be instituted immediately, upon the first serious suspicion of malaria (the patient's blood specimens are taken prior to treatment, but treatment is commenced before the tests are ready).

The initial dose is 0.1 g of acrichin intravenously (2.5 ml of a 4 per cent sterile solution, very slowly). The same dose may be administered in 20 ml of a 40 per cent glucose solution. Directly after this 0.2 g of acrichin is injected intramuscularly (5 ml of a 4 per cent sterile solution). After 6 or 8 hours an intramuscular injection of 0.3 g of acrichin is performed (7.5 ml of a 4 per cent solution).

Bigumal is administered on the first day in increased doses—0.8 g in portions of 0.2 g perorally over 6- or 8-hour intervals.

The treatment is usually continued up to 7 days. From 0.1 to 0.15 g of bigumal is slowly instilled intravenously (i.e., 10-15 ml of a 1 per cent solution of bigumal hydrochloride, or 5-7.5 ml of a 2 per cent solution of bigumal acetate), over a 5-minute period. The total daily dose of bigumal, when administered intravenously, is lowered to 0.45 g (i.e., the intravenous 0.15 g is supplemented by another 0.3 g per os).

The solution has to be warmed up before injection, as bigumal crystals are precipitated in cold solutions.

Quinine in the treatment of pernicious malaria: on the first day the patient is given 2-2.5 g divided into 2-3 portions for intravenous injection. At first 0.25 g (5 ml of a 5 per cent solution) of quinine hydrochloride is

infused intravenously very slowly (over a 3-minute period). After this an intramuscular or deep subcutaneous injection of quinine dichloride is performed (0.5-0.75 g of the substance, i.e., 2-3 ml of a 25 per cent solution). The remaining amount of quinine is also injected either intramuscularly or subcutaneously 8-10 hours later.

Parenteral administration of chloroquine is highly effective in pernicious forms of malaria. A 10 ml dose of a 5 per cent solution (0.3 g of basic substance) of chloroquine diphosphate (resoquin) is injected intramuscularly, or 5-7.5 ml of a standard ampoule solution of chloroquine sulfate (nivachin B) containing 0.040 g of the base per ml. If necessary, the injection is repeated in six hours.

Upon stable improvement and return of consciousness therapy is continued by peroral administration.

### **SYMPTOMATIC THERAPY IN PERNICIOUS (COMATOSE) MALARIA**

In cases of pernicious (comatose) malaria specific therapy is not enough—symptomatic therapy must by no means be neglected.

The following therapeutic measures are recommended for comatose conditions:

- 1) Infusion of physiological salt solution, up to one litre with adrenalin;
- 2) Infusion of 30-50 ml of a 40 per cent solution of glucose simultaneously with the subcutaneous injection of 10 units of insulin (to combat the consequences of dystrophic changes in the liver);
- 3) Spinal puncture for decreasing intracranial pressure in order to control encephalopathies;
- 4) Repeated injections (depending on pulse) of caffeine, cordiamin, strophanthin (0.5-1 ml of a 0.05 per cent solution intramuscularly) to avoid danger of cardiovascular failure. We wish to emphasise in particular that intravenous infusions of acrichin or quinine must be preceded by caffeine injections, as the latter are a safeguard against complications during the infusions;
- 5) Upon the appearance of algid symptoms the patient is warmed with hot water bags;
- 6) In comatose shock blood transfusion is recommended (250 ml); indicated also is the intravenous injection of 1.5-2 g of urotropin (for desintoxication of the preparation).

### **TREATMENT OF MALARIAL HEMOGLOBINURIA (BLACKWATER FEVER)**

Therapy is extremely urgent. The general measures employed are anti-shock agents (sympathol, morphine, cardiovascular stimulants). In acute anemia blood transfusions are done (200-300 ml), alkalis are prescribed, as well as subcutaneous and intravenous infusions of physiological salt

solution and glucose, 10 per cent calcium chloride (infuse slowly!). For anuria the entire body must be kept warm, diathermy applied to the kidney area, and a parenteral novocain block instituted. Anti-anaphylactic therapy comprises 2 injections of 50 to 75 mg of cortisone daily, or peroral administration of meticorten, prednisolone, triamcinolone twice a day in 20-25 mg doses, or dexamethazone 3 mg twice daily. It is necessary to strive for a cure of the malarial infection, as a relapse of the latter might provoke a relapse of the hemoglobinuria fever. The drugs of choice are those commonly given for *P. falciparum* and *P. vivax* infections (quinine and plasmocide are contraindicated).

### **SPECIFIC MANAGEMENT OF MALARIA THERAPY IN CHILDREN**

Children are treated according to the same basic principles and with the same preparations as adults are. Very young children may refuse to take bitter-tasting quinine, therefore a tasteless derivative of this substance may be offered — euquinine (quinine ethylcarbonate which contains 80 per cent of basic quinine); however, the euquinine doses must exceed quinine doses by 50 to 100 per cent, otherwise the efficiency of the treatment will be very low. Children take acrichin (quinacrine) unwillingly; this drug may be given to children younger than 4-5 years of age with jam. The daily dose is divided into two parts. Prescriptions for solutions should contain no more than ten single doses: for instance, a 1½-year-old is given one teaspoonful of a solution of 25 g acrichin in 50 ml water. Corresponding parts of acrichin tablets may also be prescribed (the tablet should be crushed and the required portion placed in a spoonful of jam).

However, the taste of the preparations or the whims of the child are often obstacles to administration of full doses — children often spit out their medicine. It is very difficult to administer the necessary dose to infants (solutions of the preparations are given from a spoon or bottle).

Reliable and rapid results are obtained with chloroquine, acrichin or quinine when injected intramuscularly. This method is particularly indicated for heavy malaria infections in childhood. As regards two-year-olds this injection is usually easy to give; care must be taken, however, to perform the injection as swiftly as possible, since upon introduction of the needle into the buttocks the child is apt to struggle and as a result the needle may break and there will be difficulty in extracting it. In order to avoid this we recommend fixation of the child in bed (better have a nurse restrain the child, and not the mother, as the latter may lose her head at the most salient moment and release the child).

R. S. Gershenovich (1947) widely employs quinine injections in the treatment of malaria in childhood; he points out that children tolerate these injections excellently. The introduction of quinine with rectal suppositories evokes tenesmus and diarrhea. Moreover, there have been reports on the poor absorption of quinine and acrichin via the rectum.

Plasmocide is not prescribed for children under one year owing to the danger of intoxication.

The incidence of intoxication of children by antimalaria preparations is not higher than among adults; however, accidents increase the incidence, and this should be borne in mind. The possibility of intoxication is eliminated by the preparation of tablets made up of plasmocide and bitter acrichin.

### INDIVIDUAL CHEMOPROPHYLAXIS

Chemoprophylaxis should be initiated 2-3 days prior to the possibility of the appearance of infested mosquitoes, or preceding arrival in malarial localities, and should terminate no earlier than 2-4 weeks after the cessation of the activities of the mosquitoes or departure from endemic malaria sites.

In hot climates, where malaria is transmitted throughout the year, individual chemoprophylaxis is conducted continuously with one of the following preparations:

- 1) Chloroquine, 0.3 g of basic substance once a week;
- 2) Amodiaquin, 0.4 g of basic substance once a week;
- 3) Chloridin (daraprim), 0.03 g once a week, or darachlor (chloroquine + daraprim), 2 tablets once a week;
- 4) Acrichin, 0.2 on two consecutive days over five-day intervals, or in the same manner 2 tablets of acrichin with plasmocide (each tablet contains 0.1 g acrichin and 0.02 g plasmocide);
- 5) Bigumal, 0.2 g twice a week, or 2 tablets of bigumal with plasmocide twice a week (each tablet contains 0.1 g bigumal and 0.02 g plasmocide).

In localities where a resistance of the plasmodia to chloridin has been noted this latter preparation is not employed.

Upon termination of individual chemoprophylaxis a prophylactic course of quinocide or primaquine is administered to exclude the possibility of infection with malaria.

Quinocide is prescribed in daily doses of 0.03 g for ten days, primaquine is given for 14 days, 0.015 g of the basic substance per day.

## LEISHMANIASIS

---

This is a group of systemic and local (cutaneous, mucosal) infections caused by protozoan parasites of the genus *Leishmania* (Ross, 1903), family *Trypanosomidae* (Doflein, 1901), order *Protomonadida*, class *Flagellata* (*Mastigophora*) (Cohn, 1853). The *Leishmania* are ovoid or round intracellular parasites possessing two nuclei, one trophic, the other locomotive.

The history of the study of leishmaniasis opened in 1897, when the Tashkent physician P. F. Borovsky discovered leishmania parasites in smears prepared with the discharge of granulating oriental sores.

This notable discovery was published in the *Journal of Military Medicine* (*Voyenno-Meditsinsky Zhurnal*) (1898, 11, 925-941). Before Borovsky many authors had described various pathogens of oriental sore (cutaneous leishmaniasis), but their findings were only the result of inexperience in bacteriology and pure ignorance: they scraped the surfaces of the sores, and thus recovered bacteria which were present as secondary infections.

In 1902, one of Borovsky's associates in the military hospital, K. Y. Shulgin, confirmed his discovery. In 1903, Wright in the U. S. A. also demonstrated the presence of the *Leishmania* in a patient. In 1909, Y. I. Martzinovsky wrote a monograph on cutaneous leishmaniasis.

In 1903-1904, the Englishmen Leishman and Donovan (the latter in India) discovered the parasites in the spleens of kala-azar patients; these parasites were identical with the bodies described by Borovsky.

From that time on a systematic study was launched, terminating in elucidation of the entire problem of leishmaniasis.

In 1922, Escomel described the American (Brazilian) variety of leishmaniasis, the most notable feature of which is its predilection for the mucous membranes.

The Sergent brothers, studying an epidemic of oriental sore in Biskra back in 1904, established that the area of distribution of oriental sore co-

incided with the area of propagation of biting sandflies of the genus *Phlebotomus*, while in 1908, Nicolle stated that dogs were the basic reservoir of visceral leishmaniasis in the Mediterranean zone.

In 1914, a special committee in India undertook the study of the part played by *Phlebotomus* sandflies in the spread of kala-azar in the country. This committee established the complete coincidence of the areas of kala-azar and the sandflies. Soon H. E. Shortt (India) established the infestation of the *Phlebotomus* flies by the flagellate stages of the *Leishmania*, the so-called leptomonads.

Extensive subsequent investigations were the means of establishing the presence of the *Leishmania* in dogs – predominantly visceral leishmaniasis, although cutaneous forms are likewise observed either as independent infections or as manifestations of visceral leishmaniasis.

The Sergent brothers and Donatien, and Parrot in Algeria (1921) succeeded in modelling the oriental sore in humans by rubbing into their scarified skin a pulp obtained by triturating *Phlebotomus* flies spontaneously or artificially infested with the *Leishmania* parasites from patients with cutaneous leishmaniasis.

Adler and Theodor in Palestine (1925) discovered the flagellate stages of *Leishmania* parasites in *Ph. papatasi*.

Signal contributions to solving the problem of leishmaniasis were made by Soviet researchers.

N. I. Khodukin in collaboration with M. S. Sofiyev confirmed the part played by dogs as reservoirs of the leishmaniasis infection. In the years 1927-29, Khodukin headed a campaign for mass extermination of dogs in Tashkent, the result being a sharp decrease in the incidence of the disease among children.

P. P. Perfilyev (1937) and P. A. Petrishcheva (1935-52) made comprehensive studies of the biology of the sandflies. A number of decisive experiments in the study of cutaneous leishmaniasis infection of the desert type were conducted by N. I. Latyshev (1937-40). Since oriental sore is widespread in the transcaspian steppes he presumed that the reservoirs of the infection were rodents. Numerous excavations of wild rodent (gerbil) burrows in the vicinity of Ashkhabad and the Murgab valley provided confirmation of the fact that the burrows of these animals were the breeding places of *Ph. caucasicus* and *Ph. papatasi* sandflies (N. I. Latyshev, P. A. Petrishcheva et al). Up to 30 per cent of the flies proved to be infested with the leishmania parasites. Latyshev studied gerbils for a long period of time in various sites and succeeded in establishing that these rodents were susceptible to cutaneous leishmaniasis.

Subsequently this researcher established, by "labelling" the *Phlebotomus* flies leaving the burrows through narrow artificial exits into which dyeing substances had been placed, that these sandflies covered distances of 1.5-2 km to human dwelling places, transmitting the oriental sore from the gerbils to man.

N. I. Latyshev and A. P. Kryukova established the possibility of spontaneous transmission of the *Leishmania* parasites from infested gerbils



to healthy ones in laboratory experiments. By these experiments they first proved that *Phlebotomus* flies were vectors of leishmaniasis.

The next step was to prove the role of the *Phlebotomus* in transmission of the parasite of visceral leishmaniasis. N. I. Khodukin easily transmitted visceral leishmaniasis parasites from dogs having this infection to *Ph. papatasi* sandflies (Fig. 27).

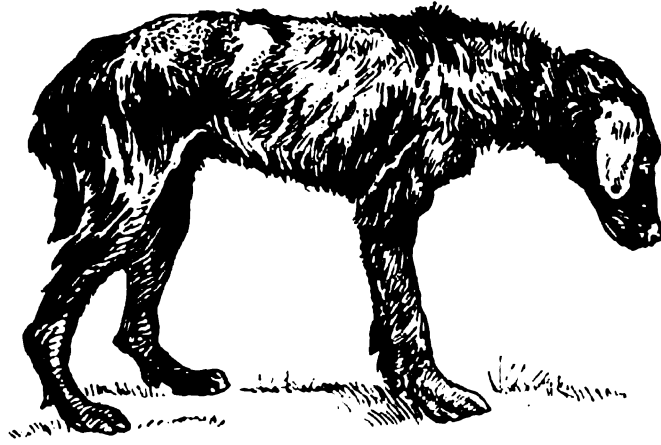


Fig. 27. Leishmaniasis in a dog

In 1942, after twenty years of fruitless labour and unsuccessful attempts, the English committee in India (Swaminath, Shortt, Anderson) finally succeeded in provoking visceral leishmaniasis in 5 healthy volunteers by feeding thousands of *Ph. argentipes* sandflies on the bodies of kala-azar patients and then exposing the volunteers to the bites of these infested flies.

Subsequently the natural reservoirs of kala-azar were clarified — dogs, jackals, hamsters, porcupines and other animals. Further it was established that in India kala-azar is transmitted from man to man via sandflies, the latter becoming infested by sucking the blood either from the skin or from the so-called late leishmanoids or papules (peculiar skin eruptions in kala-azar).

As regards clinical discoveries the following dates are noteworthy.

In 1910, Manson proposed treating kala-azar with antimonial preparations. In 1915, Di Cristina and Caronia first employed antimony for the treatment of kala-azar in Italy, M. I. Slonim did the same in 1920 in Tashkent. In 1929, I. A. Kassirsky first proposed and introduced into practice the method of sterile puncture for diagnosing kala-azar. In 1936, N. A. Mirzoyan discovered the primary lesion (see lower) in kala-azar, and in 1951-53 he proposed a short and efficient course of treatment of leishmaniasis with increased doses of sodium stibogluconate.

### VISCERAL LEISHMANIASIS

Synonyms: children's leishmaniasis, kala-azar, internal leishmaniasis (Russ.); leishmaniosis visceralis (Lat.); visceral leishmaniasis, infantile leishmaniasis, kala-azar, kala-dukh, kala-ywar, tropical splenomegaly, black

sickness, dum-dum fever (Engl., Ind.); tropische Splenomegalie, Eingeweide-Leishmaniose (Germ.); leishmaniose viscerale, leishmaniose infantile (French); leishmaniosis visceral, leishmaniosis infantil (Span.).

### Etiology

The pathogen of visceral leishmaniasis is *Leishmania donovani* (Laveran a. Mesnil, 1903). Its synonyms are: *Leishmania infantum*, *Leishmania chagasi*, *Leishmania canis*, *Leishmania nilotica*.

This parasite belongs to the *Trypanosomidae* family, class *Mastigophora* (*Flagellata*), phylum *Protozoa*.

The parasite exists in two stages: in the human body or the body of vertebrate animals it is rounded or ovoid, resembling an egg or grain of rice (Fig. 28). Its length is 3.5 microns, its width 1.5-3 microns. With the Romanovsky stain the dark-purple 0.7-0.8-micron principal nucleus (the trophonucleus) and the supplementary nucleus — the blepharoplast (kinetopole or kinetoplast) — are clearly visible. The latter usually appears in the form of a dark-purple dot or rod usually located laterally, on the equator, or at one of the poles of the parasite. The protoplasm stains greyish-lavender and its contours are commonly well defined.

The parasites habitate the spleen, liver, lymph nodes (mostly in the macrophages), sometimes they lie freely.

The leishmania multiply by longitudinal division, sometimes arranging themselves into rosettes, erroneously called schizogonic colonies.

**Cultivation.** Leishmania parasites are cultivated on many media, but the best is the well-known medium NNN (Novy-Neal-Nicolle), containing defibrinated blood.

The best method for growing *Leishmania* cultures is to seed the medium with bone marrow or spleen puncture material; positive results may likewise be obtained with blood cultures. The optimal temperature for growth of the *Leishmania* is between 22 and 30 °C.

The flagellate forms develop on the third or fourth day of cultivation (Fig. 29).

The flagellate forms also develop in the *Phlebotomus* vector. The parasite assumes a cigar-like shape (up to 20 microns long and 5 microns wide), with the trophonucleus in the thicker middle part and the blepharoplast at the anterior pole from which a long, free flagellum extends (leptomonad stage).

**Experimental infection.** Many species of wild, domestic and laboratory animals become infested with the kala-azar pathogen naturally and under conditions of experiment. Among these animals are monkeys (macaques), different species of hamsters, also gophers, gerbils, dogs, jackals, mice, etc. The experimental infection is introduced into the liver, intraperitoneally or intravenously.

In native conditions the hosts of leishmaniasis infection are dogs, jackals, and certain other animals among which spontaneous leishmaniasis has been discovered, and also man (particularly in kala-azar).

According to recent data, kala-azar is subdivided into two forms, anthroponomic and zoonomic (natural endemic foci). In desert areas, as, for instance, in Sudan, infection has been registered among military troops dislocated in uninhabited sandy deserts; the disease is also contracted by new settlers in uninhabited areas. The natural reservoirs of leishmaniasis in the kala-azar sites of Central Asia and the Mediterranean countries are evidently dogs, while in China and Brazil the reservoirs are both dogs and man. The majority of authors identify the pathogen of this form of leishmaniasis, *L. donovani*, with *L. canis*. However, it should be borne in mind that dogs infected with *L. canis* manifest cutaneous symptoms of leishmaniasis.

### Epidemiology

Sandflies are the vectors of cutaneous and visceral leishmaniasis. These sandflies are classified as belonging to the genus *Phlebotomus*, family *Psychodidae*, order *Diptera*.

*Phlebotomus* flies populate the hot and warm zones of all the continents. The northern border of their geographic distribution is defined by the cumulative warmth required for the development of at least one generation. In Asia and Europe the most northern species of sandflies (up to 48° N. lat.) is *Ph. chinensis*. *Phlebotomus* sandflies are common to all the countries of southern Europe and Asia; on the American continent they are encountered up to 40° N. lat. The highest altitude above sea level in the U. S. S. R. where *Ph. chinensis* is encountered is 2,900 m; in Peru *Ph. peruvensis* has been found at altitudes of 3,200 m, in India *Ph. papatasii*, *Ph. major* and *Ph. minutus* v. *montana* are encountered 3,500 metres above sea level in the Himalayan mountains.

The known number of species of sandflies habitating all over the world at present exceeds 300; 127 species and 34 varieties are known in the Old World and approximately 150 species on the American continent.

According to the latest classification compiled by Theodor all the Old World sandflies belong to two genera, *Phlebotomus* and *Sergentomyia*: the first comprises representatives of *Ph. papatasii*, *Ph. sergenti* and *Ph. major* groups, the second includes all *minutus* sandflies. The American sandflies belong to the genera *Lutzomyia* and *Brumptomyia*.

Theodor divided the genus *Phlebotomus* into 9 subgenera, and the *Sergentomyia* genus into 3 subgenera.

Comprehensive studies of various species of sandflies are carried out by entomologists of the Soviet Union and other countries; the insects are differentiated according to definite entomologic features (structure of reproductive organs, gullet, etc.) (Fig. 30).

Twenty-four species have been established in south-eastern Europe (A. V. Dolmatova). The *Phlebotomus* are thermophilic sandflies. Their propagation is restricted by a number of climatic factors: the atmospheric temperature must be no lower than 18 °C for a period of 4 months, while during the cold seasons the mean temperature must not be lower than

minus 6°, although the flies may survive even when the temperature falls as low as minus 20° on some days.

The *Phlebotomus* are small yellow-brown, two-winged insects 2-3.5 mm long; their bodies are densely covered with hairs and scales. The females feed on human blood and the blood of domestic and wild animals (reptiles, small rodents).

In Central Asia the first generation swarms out of its wintering quarters beginning with May, sometimes at the end of April; swarming occurs somewhat later in the Crimea and the Caucasus—at the end of May and

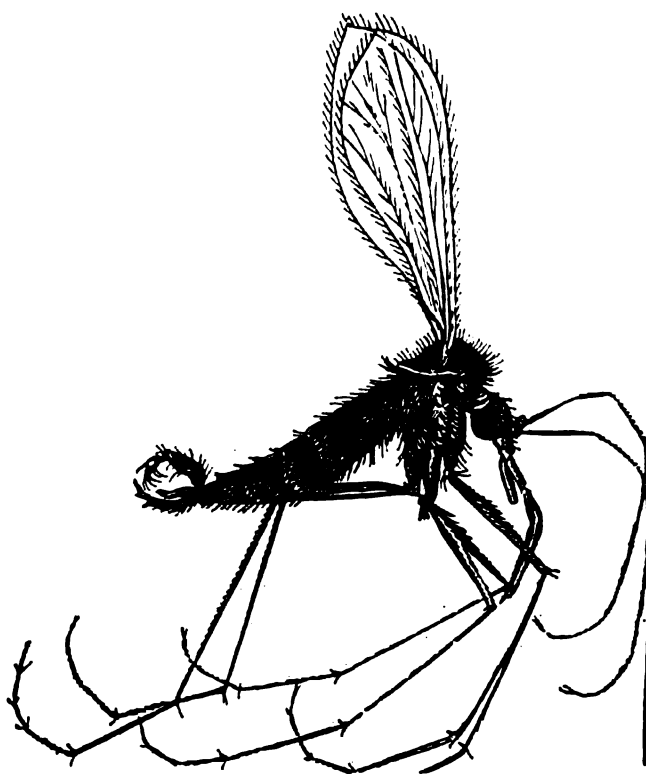


Fig. 30. *Ph. chinensis*, vector of leishmaniasis

during the first decade of June. The female lives approximately three weeks. After laying about 40 to 50 eggs it usually perishes; part of the females (20 per cent) ingest blood again and lay another batch of eggs.

Maturation of the sandfly from the egg takes 45-55 days (from ova to larva 1-7 days, I, II, and III larval stages 28-35 days, and pupal stage 10-12 days) (Fig. 31).

The favourite breeding places of sandflies are cellars, wall-cracks, moderately humid places, styres, garbage dumps, lavatories, weed-grown soil, etc.; in natural conditions the flies breed in rodent burrows where they feed on the blood of gerbils and bandicoots (*Nesokia*) while the larva feed on excrements in bird-nests, caves, etc. (Figs 32 and 33).

In caves and rodent burrows where the annual temperature is stable (+15°C in the winter) sandflies breed all the year round. They winter in the IV larval stage. The number of generations depends on climatic conditions.

Sandflies are twilight insects. During the day they keep to shady, quiet spots protected from wind. They swarm out of their shelters at sundown, and their activities continue until morning, but their assault on human beings is most vigorous up to midnight and at dawn.

The principal vectors of kala-azar in the U. S. S. R. are *Ph. chinensis* and *Ph. kandelaki*, in India *Ph. argentipes*, in China *Ph. chinensis* and *Ph. sergenti* v. *mongolensis*, in the Mediterranean zone *Ph. perniciosus* and *Ph. perflievi*, in Sudan *Ph. langeroni* v. *orientalis*.

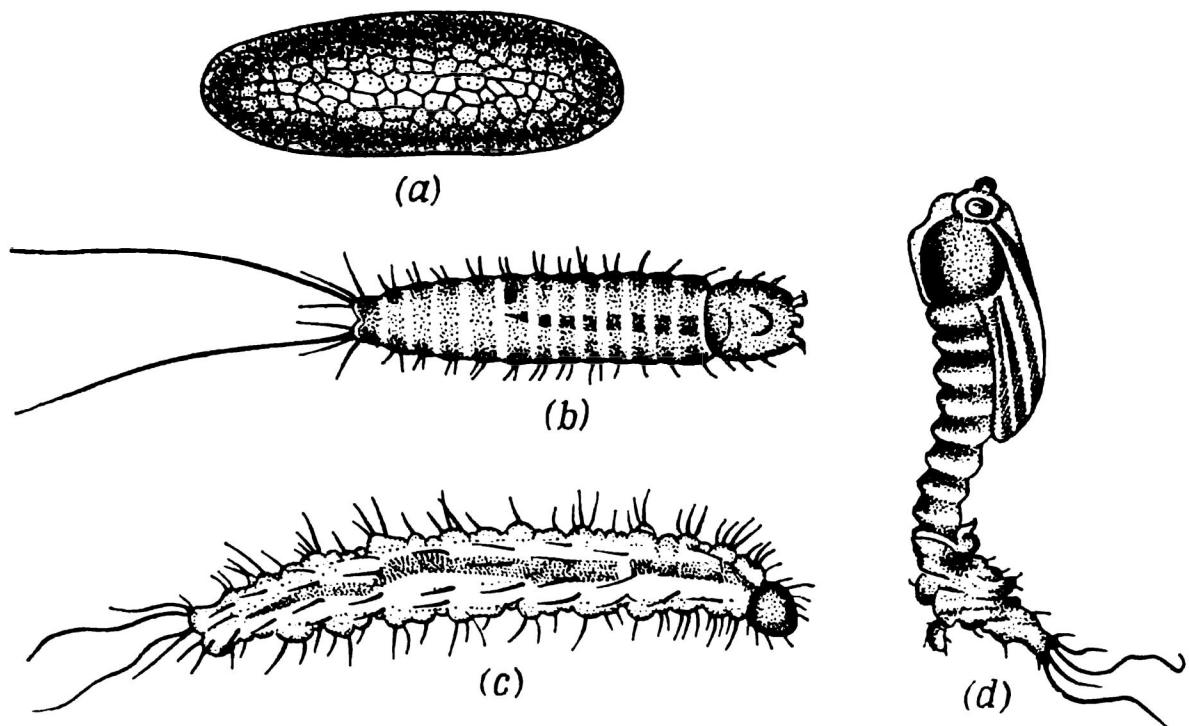


Fig. 31. Stages in the life history of mosquitoes  
a—ovum, b—larva, stage I; c—larva, stage IV; d—pupa (P. P. Perflyev)



Fig. 32. Habitat of mosquitoes: burrows of gerbil *Rhombomys opimus* in hillocks near Ashkhabad (from P. A. Petrishcheva)

Sandflies acquire the leishmania by biting leishmanoid areas of skin or upon ingesting the blood of men or animals infested with the protozoans. The leptomonad stages of the leishmania develop in the anterior





section of the alimentary tract of the sandfly. The leptomonad forms multiply and migrate to the gullet; by the seventh day they penetrate into the mouth of the sandfly. Infection of man occurs when the sandfly punctures his skin to withdraw blood. Some authors hold that infection takes place when an infested sandfly is crushed and the leptomonads penetrate into the scratched area (in any case, this does occur in experiment).

### Geographical distribution

The geographical distribution of visceral leishmaniasis is coincidental with the borders of the areas inhabited by certain species of *Phlebotomus* vectors.

An extensive leishmaniasis site is India, particularly the valleys of the Ganges and Brahmaputra rivers, Bengal, and the region north of the Hindustan plain, stretching approximately to 80° E. long., the south-eastern coast of Hindustan, the state of Madras (Fig. 34). In India the vector of kala-azar is *Ph. argentipes*. The incidence of visceral leishmaniasis is particularly high in Eastern Pakistan, where several thousand precisely diagnosed cases have been registered within ten years. Sites of the disease exist on the Indo-China peninsula and on the Sunda Isles. Although people of all ages contract the disease, children are affected less often than adults. No leishmaniasis has been noted in dogs in these areas.

*African kala-azar* (leishmaniasis of adults) is prevalent in southern Sudan, in Ethiopia, Kenya, Nigeria, Cameroon, Senegal, and other areas. The African form is most resistant to treatment and calls for prolonged therapy.

*Visceral leishmaniasis among children and adults is observed in China*, where there are great numbers of *Phlebotomus* sandflies — as many as 20 species, among them *Ph. chinensis*, *Ph. sergenti v. mongolensis*, *Ph. kiangsuensis*.

Formerly leishmaniasis was not extensively studied in China, therefore no reliable statistics are available. With the improvement of public health services in the Chinese People's Republic the registration of leishmaniasis cases has also improved. In the 1950-53 period 220,000 kala-azar patients were diagnosed and cured in the endemic regions of Eastern China alone. Visceral leishmaniasis is chiefly distributed in the north-eastern regions of China, where kala-azar is the predominant form. Visceral leishmaniasis is widespread in the vicinity of Pekin and is particularly prominent in the provinces Shan Tung, Hu Nan, Ho Peh, Kiang Su, on Taiwan; mainly children are affected. Dogs are widely infected with leishmaniasis (in Pekin 27 of 2,474 inspected dogs, in Hang-Chow 59 of 100; L. M. Isayev, 1957).

The Chinese form of leishmaniasis responds to treatment quite readily (Tchung, Hwai-Seng, 1954).

*Infantile leishmaniasis* is widespread along the entire northern coast of Africa (Morocco, Algeria, Tunis, Libya), as well as in Ethiopia, Sudan, and other areas; in the Near and Middle East the infection is common in

Turkey, Egypt, Israel, Jordan, Lebanon, Iraq, Iran; in southern Europe in Greece and the Greek Archipelago, Crete, Cyprus, Bulgaria, Yugoslavia (Macedonia, Dalmatia, and Chernogorye total up to 700 cases annually), southern Hungary, Italy (particularly Sicily and Sardinia), France (its

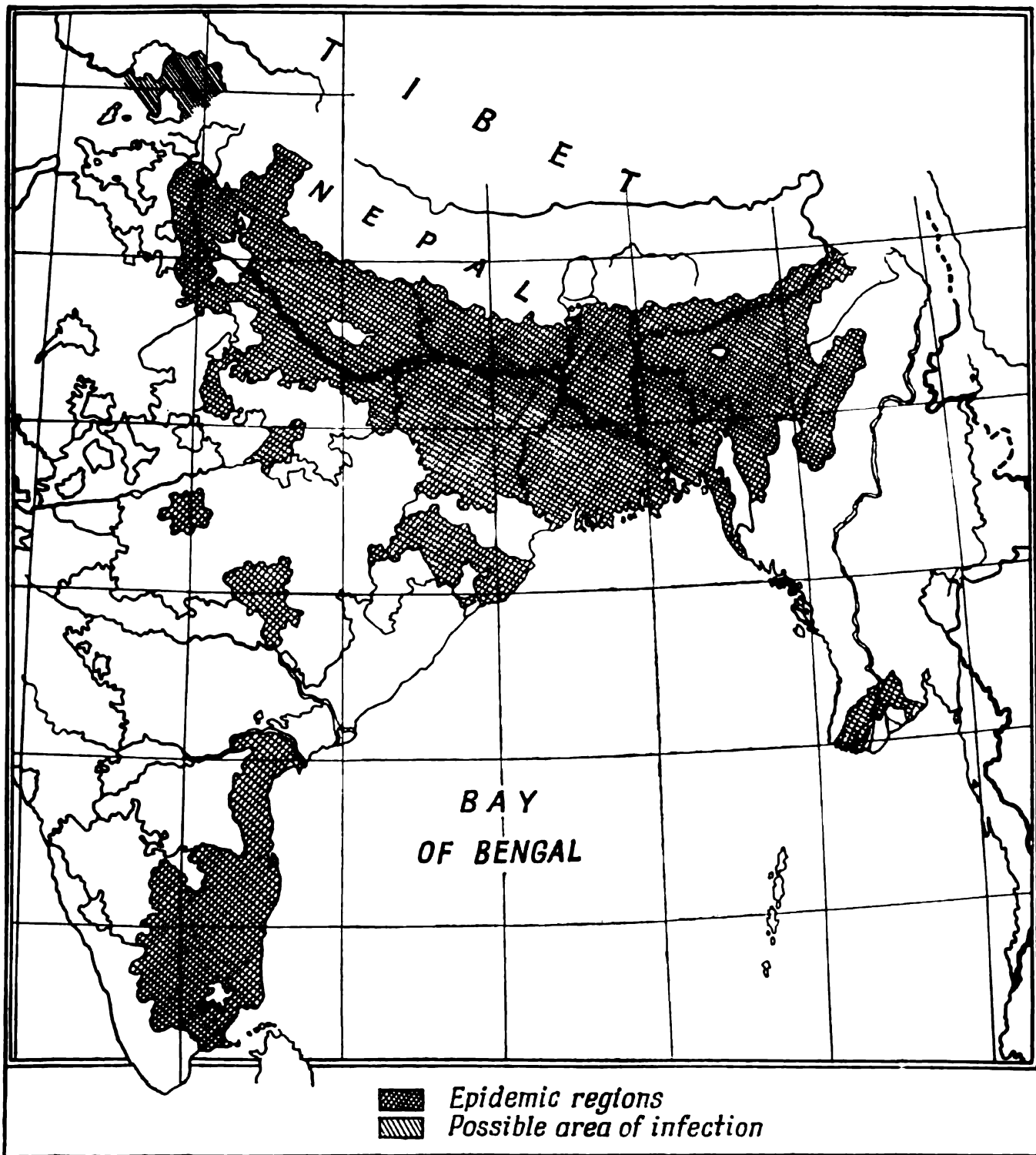


Fig. 34. Geographical distribution of kala-azar in India and Burma

southern part and Corsica), Malta (up to 800 cases a year), Spain, Portugal (1,500 cases a year in each). In general the number of patients registered every year in these countries varies between several hundred and several thousand.

Visceral leishmaniasis is rarely encountered on the American continent. We have been shown cases in New York clinics where the infection had



been brought in from Italy and the Middle East. Local sites of visceral leishmaniasis have been registered in Guatemala, Venezuela, the forest regions of Brazil, Bolivia, Paraguay and Argentina.

In the Soviet Union infantile leishmaniasis has been observed in the Central Asia republics.

The incidence of visceral leishmaniasis has decreased sharply within the last two decades.

A significant part of the adult population of India and other countries possesses a natural immunity against kala-azar. Visceral leishmaniasis rarely affects the adult population of Central Asia and the Mediterranean areas. Evidently infantile leishmaniasis is not so easily contracted by children either. Cutaneous leishmaniasis produces no immunity against infantile leishmaniasis and kala-azar.

Persons who have had visceral leishmaniasis and kala-azar evidently acquire a stable and prolonged immunity; practically no re-infections are observed.

### Clinical aspects

As has already been stated, the principal difference between the two forms of visceral leishmaniasis—kala-azar and infantile leishmaniasis—lies in their epidemiology; although certain differences are also observed in clinical findings.

Leishmaniasis of adults, kala-azar (kala-dukh, kala-ywar), which means, when translated from Sanskrit, *black, pernicious* disease, is an adult disease, and only in 5 per cent of cases does it affect children and adolescents; it does not affect dogs. The disease is characterised by the secondary appearance of dermal leishmanoid papules harbouring the *L. donovani* parasites, and also some degree of circulation of the leishmania in the blood (this explains why the *Phlebotomus* sandflies are predominantly infested through skin lesions).

Mediterranean leishmaniasis is a childhood disease; however, 1-2 per cent of patients are adults (I. A. Kassirsky, V. M. Mozheiko, and A. V. Fedulov, 1925).

Generally speaking, both kala-azar and visceral leishmaniasis are parasitic reticuloendothelioses with a characteristic clinical syndrome: irregular protracted fever, splenomegaly and hepatomegaly, anemia and granulocytopenia.

*Incubation period. Sites of access.* It has at present been established that the minimum incubation period of the infection is 3 months, the maximum—one year, on the average—6-8 months. N. A. Mirzoyan (1953) succeeded in proving this point on the basis of a study of child morbidity among children born both in the epidemic period (May-October) and in the non-epidemic period (November-April).

Mirzoyan made a detailed study of 1,280 case histories, establishing that the disease had first appeared in December, January, February, March, and April (according to anamnesis) in the majority of patients. If we consider that the December and January waves of the disease are due to

infection contracted in May or June, the spring wave is then the result of infection in the late autumn (the *Phlebotomus* sandflies swarm until October). When the clinical picture of a disease is unclear during these months in the Mediterranean zone, leishmaniasis should be suspected.

It has at present been established and confirmed by the finding of leishmania parasites that there exists a primary lesion in visceral leishmaniasis (N. A. Mirzoyan). This is the area of the bite of the sandfly, where a firm nodule develops, outerly resembling the papular form of cutaneous leishmaniasis.

The size of the nodule may attain that of a lentil; it is light-pink, slightly pigmented. Occasionally a small scale may be observed on its surface. The parasites are commonly demonstrable in skin scrapings taken before manifest symptoms of the disease have appeared; when the disease has progressed the leishmania are found much less frequently. The primary lesion is rarely discovered in children over three years of age, but it is very common in children up to 1-1½ years old. The course of infantile visceral leishmaniasis subdivides into three periods: initial, anemic-splenomegalic, and cachectic or terminal periods.

The period of recovery is also important (V. P. Petrov, 1935) in so far as treatment leads, as a rule, to complete recovery in 93-95 per cent of cases when it is instituted early and properly managed; spontaneous recovery is observed in 0.5 per cent of patients.

*Initial period.* The onset of visceral leishmaniasis is usually very insidious; however, quite soon a general weakness appears accompanied by adynamia, pallor of the skin and mucosa, loss of appetite, slight enlargement of the spleen. These symptoms are followed by an elevation of temperature.

During the first days or weeks of the disease—in slow courses—the red blood picture shows no great changes; as regards the white blood, it may at first also show a normal leukocyte count during some complication (pneumonia), or even moderate leukocytosis. The ESR is accelerated.

*Period of complete unfolding of the disease.* At the height of the disease the temperature rises, acquiring the specific characteristic of visceral leishmaniasis.

Usually an irregular or remittent fever is observed, but in solitary cases a subfebrile temperature may be maintained (up to 37.8° in the evening and normal in the morning), or, quite the opposite, it may become hyperpyrexial (up to 40-41°) (Fig. 35). In 10 to 20 per cent of cases the fever is characterised by two elevations during the day with subsequent falls, the so-called Rogers type of temperature curve in kala-azar (Indian leishmaniasis).

The authors have observed extremely rare cases of leishmaniasis in children with marked splenomegaly when the temperature was normal for a prolonged period (2-3 months).

The next symptom of visceral leishmaniasis is splenomegaly. It is usual for the spleen to enlarge rapidly both in children and adults and to become very hard (Figs 36 and 37).

The spleen extends in all directions, but particularly dextrally and caudally; this enlargement may be so great that in neglected cases the medial edge of the organ protrudes beyond the median line to the right, its lower edge reaching the pubis. The spleen is usually not painful, but when its capsule stretches significantly adult patients note a dull pain or discomfort in the left side of the abdomen.

Liver enlargement is not, as a rule, as intensive as that of the spleen; however, cases of enlargement of the liver have been observed that even surpass the spleen growth.

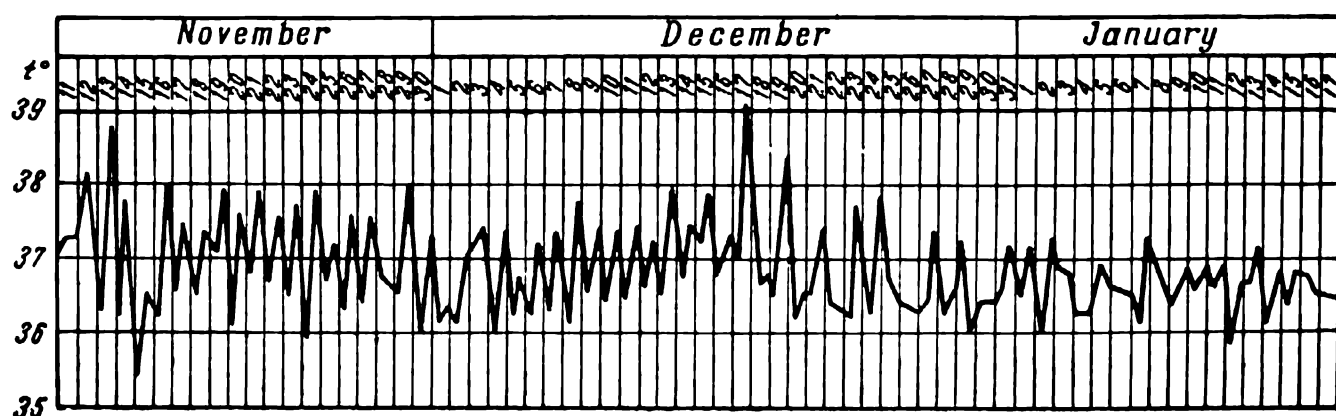


Fig. 35. Temperature curve in visceral leishmaniasis

It is interesting to note that in distinction from many diseases (malarial splenomegaly, tuberculous splenomegaly, the hepatolienal syndrome, etc.) in leishmaniasis the dimensions of the spleen and liver soon reduce under the effect of treatment; even in patients with intensive splenomegaly the spleen returns to normal after treatment (Figs 38 and 39).

Enlargement of the superficial lymph nodes is frequently observed in leishmaniasis.

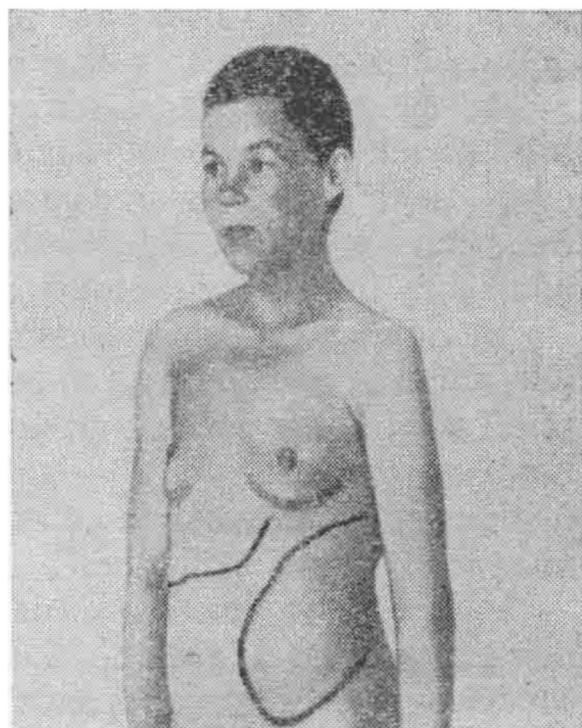
*Cachectic period.* Marked splenomegaly is associated with general emaciation, muscular atonia and thinning of the abdominal walls; therefore the spleen sags and the abdomen protrudes sharply forward.

In India, Sudan, rarer in China (in certain regions) extensive nodular lesions—dermal leishmanoids—appear on the face and other parts of the body in a small part of patients (10 per cent); there are cases either untreated during the first phase of the disease, or cases in which the lesions appear some time (several months, more frequently a year or even more) following discontinuation of therapy. These lesions are either lentil-sized nodules, sometimes small papillomas, or erythematous spots, or areas of decreased pigmentation (Fig. 40). Such cutaneous elements may persist for several years (even decades), and they contain the leishmania parasites. Actually these skin lesions are the principal source of infestation of the *Phlebotomus* sandflies with the *Leishmania* in India, Sudan, and certain regions of China (it is known that reservoirs of the kala-azar infection in these countries are not dogs, but human beings).

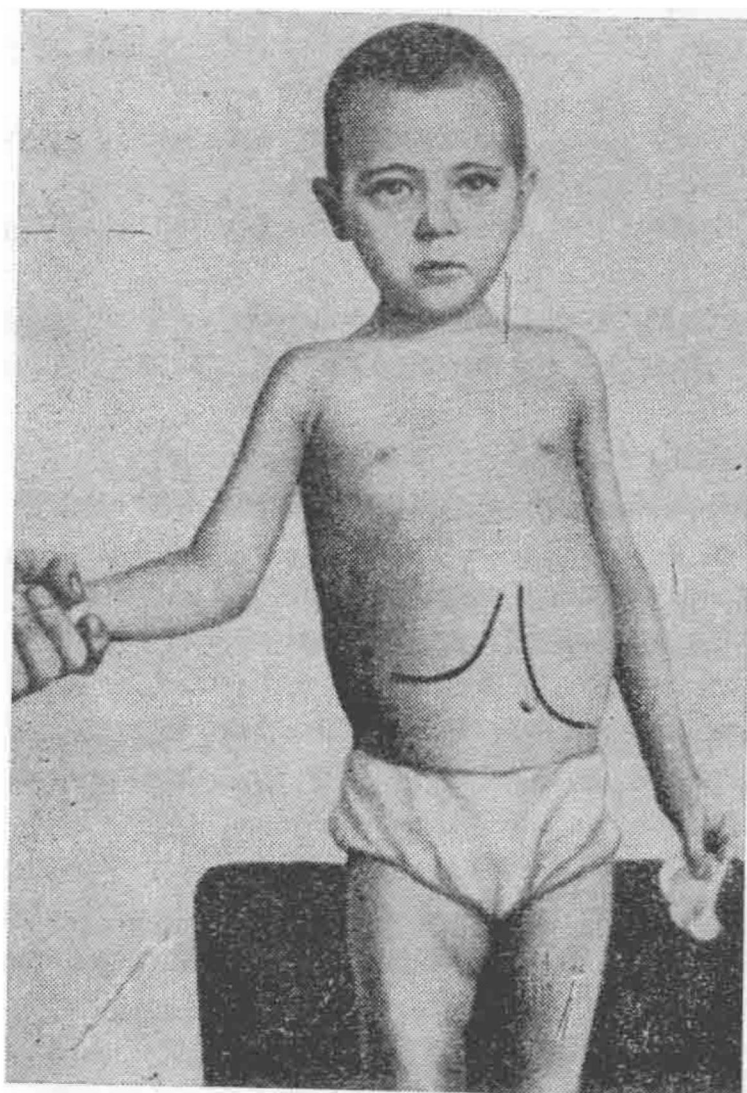
Leishmanoids are never formed in infantile visceral leishmaniasis (not to be confused with the primary lesion—a solitary early papule in the area



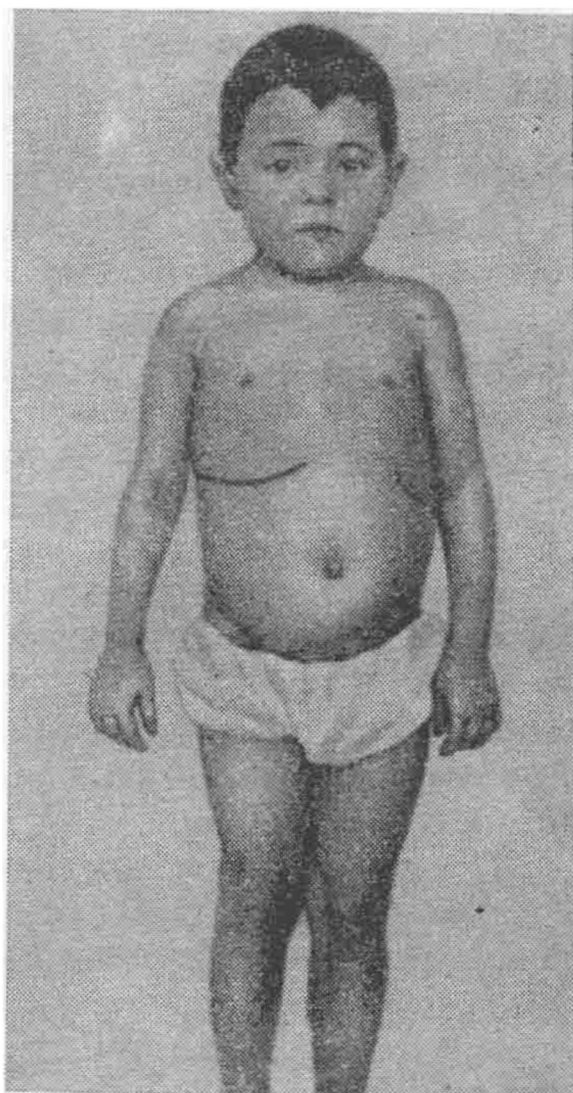
**Fig. 36. Splenomegaly in child leishmaniasis patient**



**Fig. 37. Splenomegaly in adult leishmaniasis patient**



**Fig. 38. Visceral leishmaniasis in child prior to treatment**



**Fig. 39. Same child after treatment**

of the sandfly bite where the infection develops; it should likewise not be confused with cutaneous leishmaniasis or oriental sore).

As the disease progresses anemia develops very rapidly. The hemoglobin percentage and erythrocyte count fall to very low levels in neglected cases. In all uncomplicated cases of visceral leishmaniasis acute leukopenia has been noted—from 3,000-2,000 to 800-600 leukocytes. This is accompanied by marked granulocytopenia.

Lymphocytes are predominant in the differential white blood count (70-90 per cent), and also monocytes. In 90 per cent of cases this is only relative lymphocytosis, but in 10-15 per cent of patients an absolute lymphocytosis is noted (S. Sabirov, 1954). Moreover, from the very onset of the disease an acute state of hypoeosinophilia is observed, terminating in aneosinophilia at the height of the disease.

In cases when leishmaniasis is complicated by pneumonia, suppurative necrotic processes, and the like, the leukocytic picture, according to S. D. Moshkovsky, either approaches normal, or else true neutrophilosis is displayed in the differential white count; this points to a pronounced stimulation of myelopoiesis with sufficient bone marrow function (S. Sabirov).

The above changes in the blood pattern are similar in both infantile leishmaniasis and kala-azar. A distinctive feature of the latter is a somewhat lower percentage of lymphocytes and a higher monocyte count (18-20 per cent—personal observations).

Leukopenia is accompanied by the development of hypothrombocytosis (50,000-80,000) and even thrombocytopenia.

Changes observed in the peripheral blood reflect the condition of the bone marrow hematopoiesis.

Increased and generalised reticular reactions associated with visceral leishmaniasis bring on the globulin displacements in blood serum so characteristic of this disease.

The above condition is manifested by increased serum flocculence, owing to which it was at one time proposed to diagnose leishmaniasis by means of the Brahmachari, formol-gel, and other tests. These changes in the serum, and also anemia, induce a sharp acceleration of the ESR in visceral leishmaniasis (up to 40-50 mm/h and even higher).

Three forms of infantile leishmaniasis are differentiated in accordance with the clinical picture of the disease: *acute*, *subacute*, and *protracted*. Four degrees of severity are noted: *mild*, *moderate*, *severe*, and *complicated* forms.

The *acute (violent)* form is comparatively rare. It affects very young children (up to 1-2 years of age). This form is characterised by a very violent and severe course, high temperature (39-39.5°) that persists for 3-4 weeks, anemia, relatively little enlargement of the spleen, and the development of complications typical of infants—pneumonia, enterocolitis, cachexia, occasionally noma.

The *subacute* form (comprising approximately 30 per cent of all cases) is observed somewhat more frequently; it is likewise characterised by a



severe course and high temperature, by general pallor of the skin and puffy face, occasionally with a waxy or porcelainous tinge. The duration of this form is 5-6 months.

The *protracted (slow)* form commonly affects older children and adults (65 per cent of cases). With proper treatment prognosis is quite favourable, recovery occurring in 100 per cent of cases.

R. S. Gershenovich (1936) distinguishes, besides the above, also several specific forms of visceral leishmaniasis in children, depending on the prevalent symptom in the clinical syndrome: the pneumonic, hemorrhagic, icteric, gastrointestinal, edematous, microsplenic, and apyrexial (extremely rare) forms.

**Complications.** Neglected or severe forms of adult leishmaniasis, and more frequently of infantile leishmaniasis, are followed by complications, a part of which have already been mentioned: pneumonia, enterocolitis, occasionally hemorrhagic diathesis, nephritis with a nephrotic component, agranulocytosis, pharyngeal edema, furunculosis, multiple abscesses.

Particularly serious are gangrenous processes in the mouth, sometimes in the intestine, ulcerative stomatitis, necrotic gingivitis, and noma.

Timely diagnosis of these complications is important for the institution of early treatment (antibiotics, local therapy, and leishmaniasis therapy).

## Diagnosis

There is usually no difficulty in diagnosing visceral leishmaniasis, particularly in the area of its distribution, where its possibility should always be considered.

Any morbid condition developing in the late autumn or early spring with the above-described symptoms (fever, enlargement of spleen, leukopenia) should alert to the possibility of leishmaniasis.

However, the final diagnosis is established by means of sternal puncture, first proposed by the authors in 1929 instead of the formerly practised splenic puncture, and currently universally accepted. This method ensures 100 per cent positive reaction—i. e., the *L. donovani* parasites are always discovered in bone marrow smears if the patient really has leishmaniasis (Fig. 41).

Diagnostic splenic punctures were formerly widely resorted to, but this method possesses a number of faults: the spleen is very small at the onset of the disease; moreover, the procedure itself is rather risky, particularly considering symptoms of hemorrhagic diathesis that may accompany leishmaniasis—cases of fatal hemorrhage have been described by R. S. Gershenovich (1933), V. I. Lysenko (1925), and other authors. The splenic capsule may be torn by even a pinpoint puncture caused by the child starting breathing deeply, or crying out.

It is quite safe to perform sternal puncture for children when the aspirating needle is provided with a special guard; it may be done at the earliest phases of the disease upon the slightest suspicion of leishmaniasis

and may be performed repeatedly if the puncture is unsuccessful. In children the thin sternum is punctured just as easily as a finger.

*Sternal puncture technique* is a well-known medical procedure. We consider it necessary to emphasise that in no case is it permissible to puncture the sternum by means of an unguarded thin needle directed from above into the jugular fossa or into the manubrium at a frontal angle.

Some authors propose puncturing the liver and lymph nodes to obtain specimens for diagnosing leishmaniasis. In certain cases, where these organs are accessible for puncture, this method may yield positive results.

*Serologic tests* in the diagnosis of visceral leishmaniasis are only of auxiliary value. The formol-gel test (Brahmachari and Napier) or aldehyde reaction produces positive results in 80-90 per cent of cases.

The most precise method for assaying the protein fractions is their electrophoretic division. A number of other reactions are also employed, among them the Chopra-Gupta, Louricret, and Chieffi tests.

*Differential diagnosis.* Visceral leishmaniasis should often be considered when the clinical features are suspicious in endemic areas in warm, tropical and subtropical zones; however, endemic cases of leishmaniasis, "syringe" infection of a few children may be observed out of leishmaniasis zones.

A mistake most easy to make is the confusion of *visceral leishmaniasis* with *malaria*. These two diseases have much in common; however, malaria does not acquire such a persistent course, such marked leukopenia or sharply positive globulin reactions. The absence of malaria plasmodia in the blood is a factor that should make the physician favour the diagnosis of leishmaniasis. Moreover, the fact that antimalaria therapy is of no avail in the patient's condition is a cause for suspecting leishmaniasis. The authors have had under their observation a five-year-old little girl who had been ill for two-and-a-half years. The clinical aspect of the disease was extremely confused: at the onset the child had been treated for malaria, but at that time no malaria had actually been present, the condition being due to the development of visceral leishmaniasis (unrecognised); during the final stage of the disease the child, after having been transfused with blood taken from her malarial mother, developed paroxysms of malaria, superimposed on the leishmaniasis course, and the plasmodia were found in her blood. However, the peculiar clinical aspect of this case led us to think of the possibility of leishmaniasis. And the leishmania parasites were indeed soon demonstrated!

At its initial stage leishmaniasis may be confused with a number of acute infections—*influenza*, *typhoidal-paratyphoidal diseases*, *sepsis*, *brucellosis*, etc.; however, by the third or fourth week the specific symptoms of visceral leishmaniasis—splenomegaly, differential blood count, sternal puncture—become perfectly clear.

Many types of splenomegaly due to systemic disorders of the blood, reticuloendotheliosis (of the Gaucher, Niemann-Pick, or splenic lymphogranulomatosis type), the hepatolienal Banti syndrome, or paratuberculous splenitis are usually easily differentiated from visceral leishmaniasis by a close study of the clinical features of the disease and by sternal and splenic

puncture. In leishmaniasis the parasites are always demonstrable in bone marrow smears; the above-listed diseases are characterised by typical cytological aspects.

However, it must be remembered that in cases of faulty bone marrow punctures the parasites may not be found in patients who present typical clinical symptoms of leishmaniasis, and this may lead to erratic treatment and neglect of the true disease.

Ecdemic cases of visceral leishmaniasis may appear in temperate zones, and therefore a careful study of anamnestic data is necessary. At the same time, when the clinical picture is typical, while the presence of the child in a zone of distribution of leishmaniasis is positively denied, the physician must trace back the case history and find out whether the child might not have been hospitalised together with a leishmaniasis patient arrived from some endemic site of this disease. In such an event *syringe infection* may have occurred.

In Central and South America (Panama, Brazil, etc.) there occurs a children's disease resembling visceral leishmaniasis (hepato-splenomegaly, irregular fever, anemia, leukopenia). This disease is called histoplasmosis or reticuloendothelial cytomycosis. Many incidences have been described. The pathogens of this disease are the parasitic fungi *Histoplasma capsulata* (*Cryptococcus capsulatus*) and *H. piriformis*.

The parasite is demonstrated in bone marrow, spleen, liver, and lymph node specimens obtained by puncture, and also in the peripheral monocytes after punctilious examination. Prognosis is, as a rule, unfavourable.

### Pathogenesis

Visceral leishmaniasis is a typical parasitic reticuloendotheliosis (G. N. Terekhov, 1930). It has been established, by experiments on hamsters, that the *Leishmania* parasites accumulate in the spleen as early as the third day after infection, in the bone marrow on the fourth day, in the liver on the fifth or sixth day. At first separate reticuloendothelial elements and then the entire histio-phagocytic system become hyperplastic. This is accompanied by reactive proliferation of reticular cells of the spleen, the Kupffer cells (star cells of the liver, or astrocytes), connective tissue wandering cells.

### Pathology

Macroscopic changes correspond to the clinical findings: anemic organs, splenohepatomegaly, absence of adipose tissue.

The morphological changes observed are reticular hyperplasia in the spleen and liver (the reticuloendothelial organs). The *leishmania* parasites are found when the autopsy is performed no later than 1-2 hours post-mortem in the reticular cells, capillary endothelium and Kupffer cells. Solitary sites of anemic and hemorrhagic infarction are found in the spleen, as well as sites of myeloid hematopoiesis and a growth of mesenchymal elements in the follicles; the reticuloendothelial cells teem with parasites. Cortical swelling and reticular hyperplasia are evident in the lymph nodes; the bone marrow shows reticular and erythroblastic hyperplasia, the liver — hyperplasia of Kupffer's cells and sites of myeloid blood formation.



## Treatment

Visceral leishmaniasis has at present become an absolutely curable ailment. However, formerly, before the introduction of antimony therapy, the mortality rate of kala-azar and infantile leishmaniasis was almost 100 per cent.

Expedient treatment of visceral leishmaniasis was made possible by the discovery of an effective agent—sodium stibogluconate (solustibosan, pentostam), manufactured under the name of solusurmin in the Soviet Union.

Sodium stibogluconate is the sodium salt of a complex compound of antimony and gluconic acid that contains 20-22 per cent of metal antimony. It comes as a white powder, soluble in water (preferably warm or hot). As has been established by N. A. Mirzoyan, this preparation may be administered daily, and in heavy doses, without undue effects.

Solusurmin (the Soviet analogue of solustibosan) is introduced intravenously or subcutaneously in 20 per cent solutions. Intravenous injections are given daily. The solution must be sterilised.

A 20 per cent aqueous solution of sodium stibogluconate becomes opalescent after filtration. Sterilisation is attained by heating over boiling water for 40 minutes. The solution is suitable for use for 2 to 4 days after preparation. It is prepared in twice distilled water. The formation of even a hardly noticeable cloudiness makes it toxic and thus unfit for use.

Solusurmin treatment with sufficient doses (worked out in Uzbekistan by N. A. Mirzoyan) is, on the average, of short duration—only 10-12 intravenous injections (Table 7). Treatment of patients with visceral leishmaniasis should be instituted as early as possible; this predetermines favourable prognosis even in acute and subacute forms of the disease, as well as in neglected cases.

Table 7

Recommended Solusurmin Dosages (after N. A. Mirzoyan)

Age and condition of patient	1st injection in g/kg	2nd injection in g/kg	3rd and subse- quent injec- tions in g/kg
1. Children under seven years with no signs of dystrophy .....	0.05	0.1	0.15
2. Children under seven years with signs of dystrophy, and/or concomitance of other diseases .....	0.04	0.08	0.12
3. Children from 7 to 14 years .....	0.04	0.07	0.12
4. Patients older than 14 years .....	0.04	0.07	0.01

*Note:* The above dosages are administered in single daily doses; adult patients are injected with two half-doses twice a day (morning and evening). It is not advisable to divide the daily dose into smaller fractions injected over short intervals.

If no considerable improvement in the patient's condition occurs after 7-8 injections the dose for children should be increased to 0.15, and for adults to 0.12 g per kg of body weight.

The mean indices showing the efficiency of treatment of patients with visceral leishmaniasis are drawn up in Table 8.

Table 8

Mean Indices for Efficiency of Treatment of Visceral Leishmaniasis with Different Preparations (after N. A. Mirzoyan)

Preparation	Total number of patients	Average duration of treatment in days	Percentage of concomitant diseases	Cured cases in per cent	Relapses in per cent	Fatal cases in per cent
1. Tartar emetic (antimony potassium tartrate) .....	120	72	139.0	71.0	—	25.9
2. Surmin (Soviet analogue of stibosan) .....	184	62	75.5	76.2	—	17.9
3. Stibosan .....	80	50	75.0	81.3	—	15.0
4. Neostibosan (given on alternate days) .....	100	37	68.0	89.0	—	11.0
5. Neostibosan (given daily) .....	72	14	23.6	87.6	8.3	4.1
6. Stilbamidine .....	58	26	46.5	88.0	7.0	5.0
7. Solusurmin (Soviet analogue of solustibosan) (dosage 0.01-0.03 g/kg) .....	222	32	59.5	81.6	5.4	9.0
8. Solusurmin (0.04-0.05 g/kg) .....	125	24	48.0	90.4	4.0	5.6
9. Solusurmin (0.1-0.15 g/kg) .....	100	12	25.0	91.0	6.0	3.0
10. Solusurmin (0.1-0.2 g/kg) .....	70	12	20.5	97.2	1.4	1.4

Besides specific treatment extensive administration of supplementary therapy is strongly advised: for secondary complications — antibiotics, for anemia — transfusion of packed erythrocytes, for noma and ulcerative stomatitis — penicillin, large doses of ascorbic acid, mouth rinses with hydrogen peroxide, potassium permanganate, glycerin.

In the subacute form of leishmaniasis the temperature usually drops on the 9th to 14th day after institution of therapy; in the protracted form unaccompanied by complications this occurs on the 15th or 16th day. Under the effect of the sodium stibogluconate injections both adult and child patients feel much better after the first few injections, their temperature

subsides by a serrated curve in 5-6 days and is restored to normal at the end of the course of treatment; the patient's face turns from pale to pink, his appetite returns. The duration of the treatment is from 8 to 22 days.

Neostibosan is the amino salt of para-aminophenyl-stibinic acid. The preparation contains 40 per cent of metallic antimony. It is administered in a 5 per cent solution intravenously or intramuscularly in gradually increasing doses. The initial dose for adults is 0.1 g of the substance, and the highest dose 0.3-0.4 g per day; for children the initial and maximum doses at various age levels are: from 1 to 3 years 0.05 and 0.1 g; 4 to 5 years 0.1 and 0.2 g; 6 to 8 years 0.1 and 0.25 g; 9 to 12 years 0.1 and 0.3 g. The total number of injections required is approximately 18 or 20.

The return of the spleen to its normal size occurs most rapidly in the early phases of the disease. In cases of intensive splenomegaly the spleen recedes to the subcostal area no sooner than in a month or a month and a half. By this time both the white and red blood elements and the protein components of the blood serum also return to normal. It is not necessary to obtain bone marrow specimens for controlling the effect of the treatment on the parasites.

Many of our patients with very severe and neglected forms of the disease (one woman had been ill for 2<sup>1</sup>/<sub>2</sub> years) were cured by a combination of persistent antimony therapy and blood transfusion. This again shows that proper management of visceral leishmaniasis therapy with specific drugs and symptomatic pathogenetic treatment ensures complete recovery even in very neglected cases for which the prognosis was formerly poor. In such neglected cases it is not always possible to attain complete normalcy of the spleen, but, as a rule, this organ recedes under the ribs 2-3-4 months after termination of therapy, provided treatment has been properly managed.

No relapses are usually observed following systematic, full-course treatment.

However, the patients require medical follow-up for a term of 4-6 months.

*Signs of recovery from leishmaniasis.* Treatment may be discontinued upon the appearance of the following signs and symptoms pointing to recovery from leishmaniasis:

- 1) complete cessation of fevers and their absence for 2-2<sup>1</sup>/<sub>2</sub> weeks following termination of treatment;
- 2) improvement in general condition of the patient, disappearance of pallor, return of normal colouring and normal turgor of the tissues, in children a return of liveliness (children affected with leishmaniasis are extremely apathic);
- 3) return of appetite;
- 4) marked decrease (almost to normal) of spleen and liver;
- 5) normal red and white blood counts, normal differential blood count, sharp decrease of the number of lymphocytes, appearance of eosinophils (1-3 per cent);
- 6) disappearance of positive formol reaction.

When all the above signs and symptoms appear there is practically no point in repeating sternal punctures.

The treatment of both adults and children is generally the same, but the former tolerate it much better than the latter, and in non-neglected cases they require a lesser number of intravenous injections.

It is important to note that individuals who have had leishmaniasis in their childhood and were cured of it 20-25 years ago are at present perfectly healthy. They show no symptoms at all of late aparasitic metaleishmaniasis, such as enlarged spleen or liver, or anemia.

## CUTANEOUS LEISHMANIASIS

---

Notwithstanding the numerous local names, at present a designation that is universally accepted is cutaneous leishmaniasis (the Borovsky disease).

Synonyms: tropical ulcer, oriental sore, Penjdeh sore (Russian): *ulcus endemicum*, *granuloma endemicum*, *furunculosis orientalis* (Latin); oriental boil, oriental sore, frontier sore, Delhi boil, Aleppo boil, tropical sore, Biskra button, Bagdad boil, Kandahar sore, Delhi sore, Delasoa sore, oriental button, Tashkent ulcer (Engl., Ind.); bouton d'Orient, clou de Biscra, bouton de pays chauds, bouton d'Aleppo (French); bottone d'Oriente (Ital.); Orientbeule, Jahresbeule (Germ.).

Cutaneous leishmaniasis has a great number of local names.

In the U.S.S.R.: penjdeh-bashi (Penjdeh ulcer, sore, or boil, named after the village Penjdeh, now Takhta-Bazar), pesheh-hurda (mosquito-bite), iyl-chyban (year-pimple, "yearling"), yaman jaragat (bad ulcer), doneh murgou (Murghab ulcer), Sart, Penjdeh, Merv, Ashkhabad and Kokand sore ("pendinka", "ashkhabadka", "kokandka"), salek ("yearling"), Yelisavetpol and Lenkoran yearling; in Greece—Delphic ulcer; in Algeria—Laghouat, Tlemcen, Tugurt ulcer and "isankr-sahari"; in Tunis—Gafsa ulcer; in Egypt: Cairo, Nile ulcer; in Yemen—Yemen ulcer; in Palestine—Jericho ulcer; in Iraq—Baghdad ulcer; in Iran—Bushire and Isfaghan ulcer; in Afghanistan—Balkh and Kandahar ulcer; in India—Agra, Bombay, Delhi, Cambay, Lahore, Meerut, Punjab ulcer; on the Philippine Isles—Phillippine ulcer.

### Historical data

Cutaneous leishmaniasis has been known to mankind for several thousand years. Mention of it is made in the Bible and in many oriental scripts.

The first scientific description of the disease was made in 1745 by the English physician Pocock, and a little later by the Russel brothers (Syria, 1756). In Russia the first description of the disease was presented by N. Arendt in a special dissertation (1862).

During that same period cutaneous leishmaniasis in the Caucasus was described by P. N. Yemelyanov, M. I. Manotskov, Y. Finkelstein and others.

An important scientific event in parasitology was the discovery by P. F. Borovsky (1897) of the pathogen of cutaneous leishmaniasis—the Borovsky bodies. Thus another name for the disease — the Borovsky disease — is perfectly justified.

After Borovsky the pathogen of cutaneous leishmaniasis was described by Wright in America (1903), and by Martzinovsky in Russia (1909).

The infection of gerbils with cutaneous leishmaniasis through the agency of sandflies in an non-endemic area was first achieved by N. I. Latyshev and A. P. Kryukova (1940), and human beings were infected by Adler and Ber (1941).

### Parasitology and epidemiology

The pathogen of cutaneous leishmaniasis — *Leishmania tropica* — belongs to the genus *Leishmania* (Ross, 1903) family *Trypanosomidae* (Doflein, 1901), order *Protomonadida* (Blochmann, 1895), class *Flagellata* (Cohn, 1853).

Morphologically this parasite does not differ from the above described *L. donovani*, but its biological and serological features are different. In cultures and in the bodies of *Phlebotomus* sandflies the parasite acquires a flagellate form (leptomonad stage).

*L. tropica* is introduced into the body with the bite of a vector, predominantly *Ph. papatasi*, *Ph. sergenti*, *Ph. caucasicus*, and others. After an incubation period of several weeks to one, two, or three years specific granulomas — leishmaniomas — appear at the site of the mosquito bite.

The urban source of infection with *L. tropica* is man, the desert type of the disease (the moist form) is derived from wild rodents (gerbils, gophers, possibly hedgehogs), dogs and man.

In the latter case the sandflies breed in the depth of gerbil burrows. It has been established that up to 500 sandflies may breed in the nest-chambers of the gerbil. Consequently, the desert form of cutaneous leishmaniasis is a natural endemic infection, a zoonotic disease that affects rodents and is transmissible to man. The period during which it is possible to acquire cutaneous leishmaniasis depends on climatic conditions; in the Kara-Kum desert it begins in the middle of April and continues through September; the most dangerous time is June, July, August. The sandflies swarm out of their shelters at dusk.

The sandflies molest man from twilight to dawn, but they are most active from the time it becomes dark to midnight.

The leishmania parasites penetrate into the intestine of the sandfly with the blood it has ingested; from the intestine they migrate to the fly's pharynx and mouth, from whence they are conveyed to the blood of a healthy person when the insect bites him, and thus the infection is transferred.

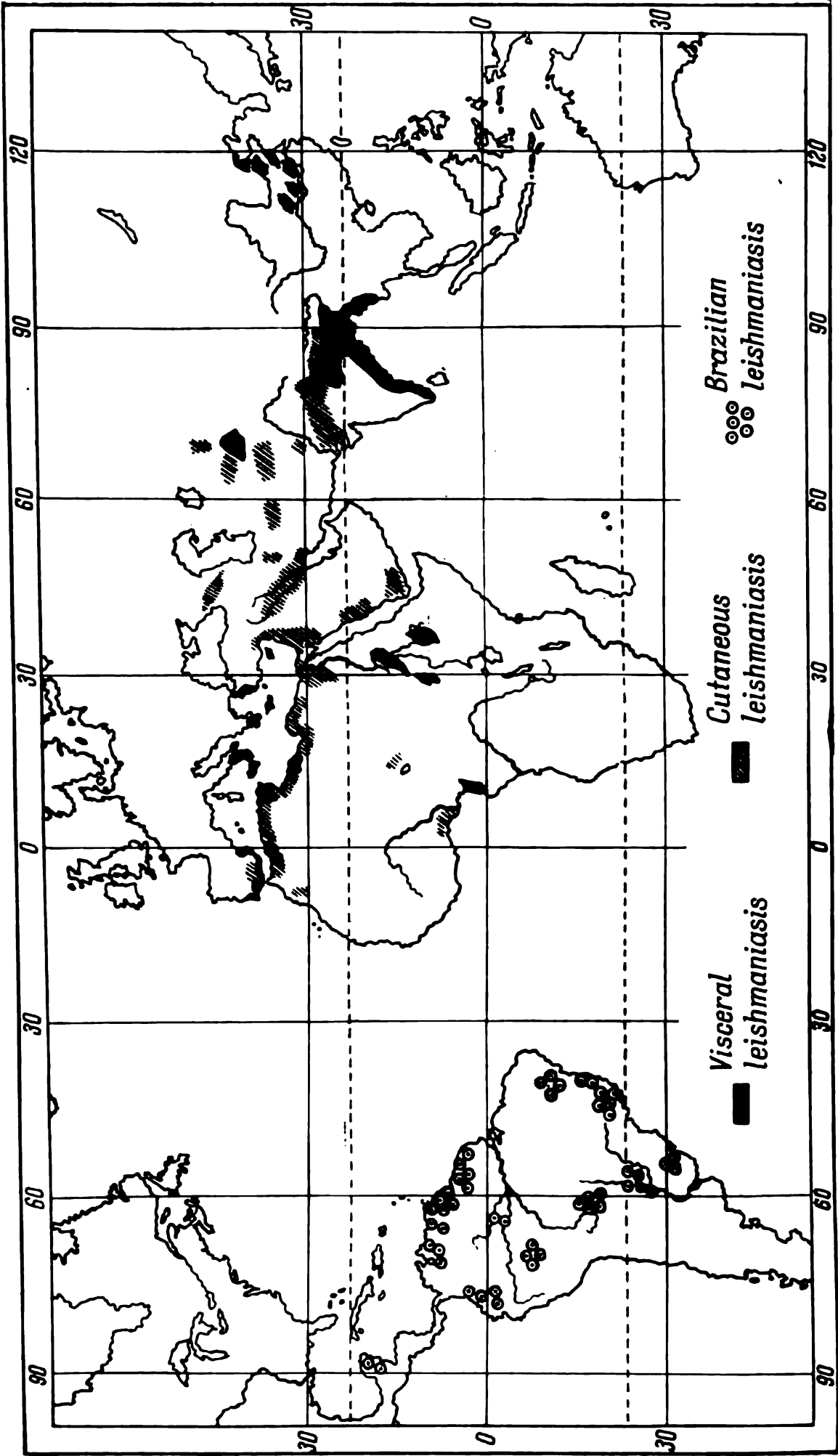


Fig. 42. Geographical distribution of visceral, cutaneous, and Brazilian leishmaniasis

## Geographical distribution

Cutaneous leishmaniasis is common to southern Europe: Spain (southern part), France (south), Italy, Greece, the islands of the Aegean Sea, Yugoslavia (Macedonia, Chernogorye, Dalmatia), the islands Crete and Cyprus; in Albania (everywhere); in Africa: Morocco (everywhere), Algeria (Biskra), Tunis (chiefly in the south—Gabes, Gafsa), Lybia, Egypt, Sudan, Ethiopia, the Republic of Tchad, Nigeria, Cameroon, Dahomey, Guinea, Angola, Ghana; in Asia: Syria, Turkey (south-eastern Anatolia), Israel, Jordan, Yemen, Aden, Saudi Arabia, Iraq (in the vicinities of Baghdad, Mosul—up to 40 per cent of the population), Iran (around Teheran, Isfahan, Meshed), Afghanistan (Herat, Kandahar), Beluchistan, India (Lahore, Meerut, Delhi, Agra, Bombay, Assam), Ceylon, Indo-China, the Philippines.

A map showing the geographical distribution of visceral, cutaneous, and American (Brazilian) leishmaniasis is presented in Fig. 42.

## Clinical aspects

The first Russian physicians already singled out two clinical forms (two types) of cutaneous leishmaniasis; the *dry* and *ulcerative* (moist) forms; however, a scientific description of these variations of cutaneous leishmaniasis, giving both the clinical and epidemiological aspects, was only set forth much later in the works of I. I. Gitelson (1933); P. V. Kozhevnikov, N. V. Dobrotvorskaya, and N. I. Latyshev (1947).

*First type of cutaneous leishmaniasis* (urban type of cutaneous leishmaniasis—Leishmaniosis typica urbana) is late ulcerating leishmaniasis (Leishmaniosis tarda exulcerans). Its pathogen is *L. tropica minor* (Yakimov, 1915). This form of the disease is prevalently observed in the towns and cities of Central Asia, South Europe, Africa, India.

The incubation period of the parasite is a long one varying from several months to one year and longer (incubation periods lasting 3-4 years have been described).

The leishmanioma (the sore or ulcer) appears as a small primary papule—an elevation of 1-2-3 mm, slightly brownish. This form mostly affects the face.

The elevation gradually grows larger and higher; bud-like projections appear. Its colour turns reddish-brown, the anterior surface takes on a dull shine. Very often a crater-like depression 1 mm deep is formed in the centre of the primary sore; it is rounded, and its bottom is scaly.

P. V. Kozhevnikov notes two characteristic features of this form of cutaneous leishmaniasis: 1) when the ulcer is curretaged to obtain a specimen for analysis a drop of serous liquid appears on its surface; 2) a fragment of the tubercle removed with a scalpel is slightly translucent.

The tubercle grows very slowly; its diameter attains 5-6 to 10-15 mm in 6 to 9 months. However, in some cases relatively large nodules (up to 2 cm in diameter) are formed within 2-3 months.



Sometimes the basic growth of the sore occurs in the deep dermal layers; in such cases a deep-lying infiltrate is palpable.

Noticeable exfoliation usually begins after 2 months. In 4-6 months a yellowish or brown crust stratified with dark-red seams (blood) is formed.

When removed the scaly crust bares a shiny surface of erosion covered with pinpoint droplets of blood.

The lesion may gradually heal at this stage. However, in the majority of cases the crust thickens and comes to look like a cutaneous horn or



Fig. 43. Cutaneous leishmaniasis on the face

psoriasis rupioides. The development of a secondary infection causes the appearance of a suppurative and serous exudate from underneath the crust.

The crust usually falls away, baring a shallow ulcer with steep or shallow edges (late ulceration takes place within 4-6-10-12 months after onset of disease). The depth of the ulcer formed on the protruding infiltrate does not ordinarily exceed 1-3 mm. In the open ulcer the exudate is usually sparse, serous, with admixtures of pus-like clots. The ulcer is encircled by an elevated infiltration ridge; the latter grows continuously, occasionally the lesions merge (Fig. 43).

It takes, on the average, one year from the appearance of the tubercle to the healing of the ulcer (hence the Russian name “godovik”, meaning “yearling”), but in a number of cases the process may continue for a longer time. Poor immunologic reactions in the organism may, under certain conditions, cause an indolent turberculoid type of cutaneous leishmaniasis (Fig. 44).

During the healing process the infiltrate gradually flattens out, granulation tissue appears in the base of the ulcer instead of the necrotic masses; epithelisation commences, and finally a residual scar is formed,

*Second type of cutaneous leishmaniasis* (Murghab cutaneous leishmaniasis, pendinka, desert-rural cutaneous leishmaniasis — *Leishmaniosis cutanea, typus rusticanus*) is the early ulcerating form. Its pathogen is *Leishmania tropica major* (Yakimov, 1915).

The average incubation period for this form of the disease is shorter than for the first type, lasting from 2 weeks to 3 months. The lesions usually affect the extremities, commonly the lower ones.

The primary symptoms have been described differently by different authors who note primary pigmentation spots, edematous papules, phlyctenules, etc.; however, all these formations develop on a flat, wide, nodulous eminence with a diameter of 5-10 mm, or on a still larger furunculoid infiltrate or boil (10-20 mm).

Fig. 44. Tuberculoid leishmaniasis; ulcerative variety.  
Leishmanias recovered  
(from P. V. Kozhevnikov,  
N. V. Dobrotvorskaya,  
N. I. Latyshev)



This boil or node is red, and it is surrounded by a slight swelling. It differs from a furuncle by being softer and only slightly sensitive to pain.

The development of the leishmaniasis tubercle progresses rapidly. A pin-head necrotic spot is formed in the centre of the lesion, a whitish spot resembling the head of a pustule. Often vesicles appear on the lesion; they soon break open, and an ichorous discharge appears; the latter dries up subsequently, to form a crust. When this crust is removed a shallow ulcer 1-3 mm across is seen.

In some cases the ulcerative process does not progress any further; the wound under the crust gradually closes and the leishmaniasis sore disappears (abortive course). However, in a greater number of cases the infiltrate continues growing and subsequently decomposes; this latter stage is characterised by the acute development of a central site of necrosis. The ulcer so formed has a jagged, sharp-cut, perpendicular edge. Meanwhile the ulcer still grows, and subsidiary sores are formed (hence the irregular shape with scalloped edges characteristic of leishmaniasis ulcers of the second type).

The ulcer may grow to 10-15 cm across. The appearance of the sore and its bed changes depending on the phase of the disease and local reactions. An intensive areola of congestion is formed around the ulcer; the

colour of this ridge changes from dirty-red to brownish; occasionally no distinct ridge is visible, it merges with the extensive, diffused cutaneous infiltrate. The progressive growth of the leishmaniasis lesion continues for 2 to 5 months, after which its resolution commences – the necrotic masses disappear and epithelisation of the ulcer occurs.

Cutaneous leishmaniasis (particularly the ulcerative form) is distinguished for its multiple aspects (the present authors have observed a great variety of atypical forms); hence a number of specific classifications have been compiled (Fig. 45).

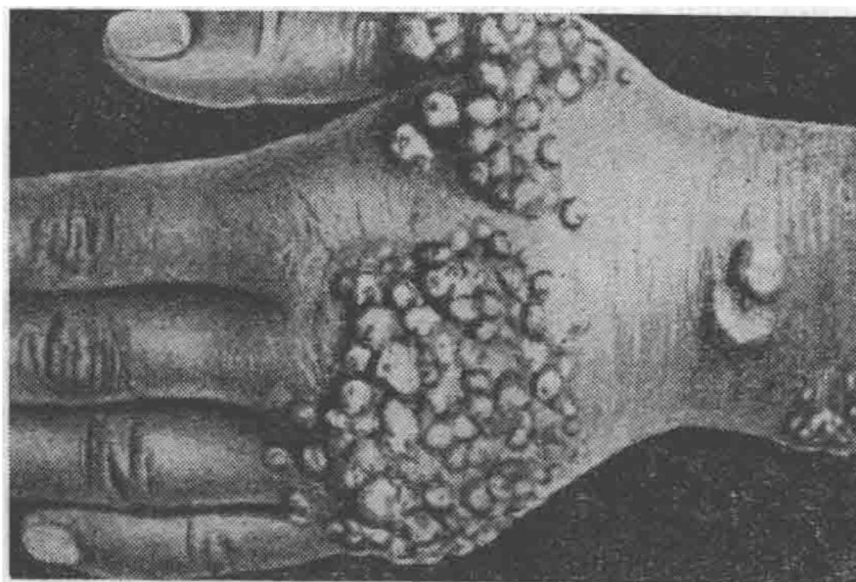


Fig. 45. Second type of cutaneous leishmaniasis. Wart-like formations. Ulcerative nodular lymphangitis (P. V. Kozhevnikov, N. V. Dobrotvorskaya, N. I. Latyshev)

P. V. Kozhevnikov (1947) cites a long list of dermatoses that leishmaniasis may imitate. It was only the persistent nature of these lesions that did not respond to specific treatment for many months that made the attending physicians send their patients for advice to corresponding clinics, where the leishmania parasites were discovered. Tuberculoid and lupoid types of leishmaniasis have been described (I. I. Gitelson, 1952). Diagnostic mistakes have also been reported, when leishmaniasis of the lower lip has been taken for cancer. Moreover, another thing that should not be forgotten is the possible development of lymphangitis both near the primary ulcer and at a distance of 50-70 cm from it.

It must be emphasised that cutaneous leishmaniasis is not always an innocuous skin disease terminating with an insignificant cosmetic defect. The formation of extensive infiltrates and ulcerating sores on the face, particularly the nose and lips, disfigure the patient; the lesion may lead to the formation of scars (for instance, in the area of the elbow, wrist, and hand joints), that impair the function of the joints to a certain degree (Fig. 46).

Moreover, it should always be borne in mind that multiple leishmaniasis lesions may develop, depending on the number of inoculations (either numerous bites of one and the same sandfly or the bites of many flies).

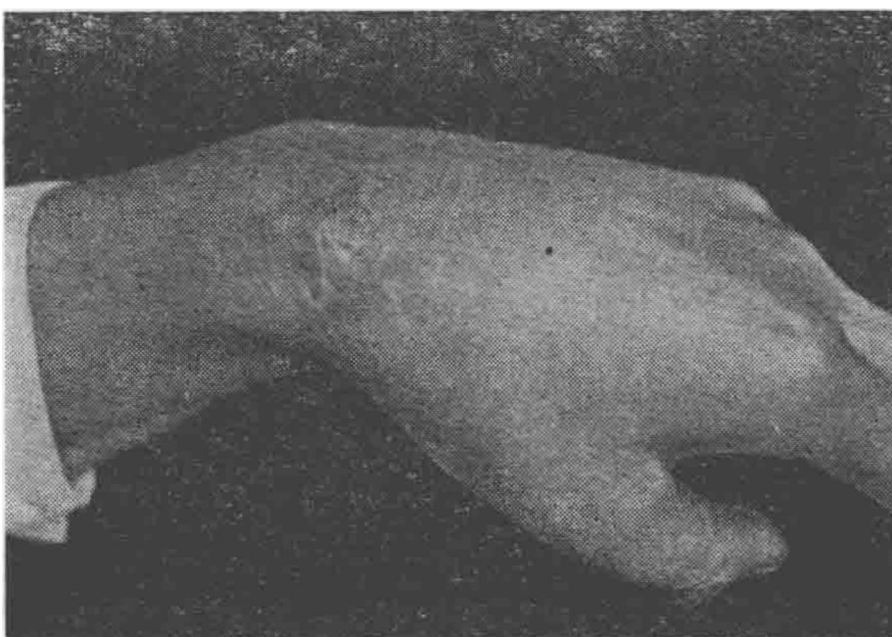
**Fig. 46. Cutaneous leishmaniasis on upper extremity**



**Fig. 47. Cutaneous leishmaniasis on lower extremity two weeks following treatment. Former dimensions of ulcer are visible.**



**Fig. 48. Scars after cutaneous leishmaniasis (oriental sore)**



The number of lesions is always greater in the ulcerative form (A. I. Slavin has observed a patient with 222 lesions, L. Geidenreich – with 174, Torres – with 248, etc.); in the urban (dry) form of cutaneous leishmaniasis the number of lesions does not, as a rule, exceed 25-30.

The lesions are most intensive on the face and the extremities. However, as people often sleep without any clothes or covers during hot, sultry nights, any part of their bodies may be bitten by the *Phlebotomus* flies. Hence the possibility of formation of ulcers in the perineal area, on the genitalia, the abdomen, buttocks, etc.

Besides cutaneous leishmaniasis the authors have observed acute skin reactions in cases of idiosyncrasy to sandfly bites, exhibiting a full pattern of varicella.

It is noteworthy that of such a great number of sandfly bites only one bite was “effective”: a leishmaniasis lesion (urban form) developed on one finger. Analogous cases have been described by Y. N. Pavlovsky (1927) and other authors.

There exist several types of scars that remain after cutaneous leishmaniasis (experienced doctors who have practised in hot climates are able to recognise by these “signs” the type of infection their patient was ill with). P. V. Kozhevnikov and N. V. Dobrotvorskaya have described scars that were almost smooth, splitted scars, scars with bridge-like contractions or keloid-like outgrowths, and weakly expressed atrophic scars (Figs 47 and 48).

In conclusion we present tables (after P. V. Kozhevnikov, N. V. Dobrotvorskaya, and N. I. Latyshev) for the differential diagnosis of the two types of cutaneous leishmaniasis.

**Specific Features of the Two Types of Cutaneous Leishmaniasis**

	<b>First Type</b>	<b>Second Type</b>
<b>Synonyms</b>	Late ulcerating leishmaniasis Ashkhabad ulcer. Kokand-ka. Godovik (yearling)	Acute necrotising leishmaniasis Penjdeh ulcer, Murghab ulcer
<b>Incubation period</b>	Protracted: usually 2-6 months, often 1-2 years	Short: usually 1-4 weeks
<b>Primary symptoms</b>	Small, normally coloured or brownish, slightly elevated papule	Noticeable, acutely inflamed, often furunculoid infiltrate
<b>Course</b>	Slow	Rapid
<b>Appearance of ulceration</b>	After a period of 3-6 and more months	In 1-2-3 weeks
<b>Lymphangitis</b>	Rare	Frequent
<b>Subsidiary sores</b>	Relatively rare	Frequent
<b>Localisation</b>	More usual on face than lower extremities	More usual on lower extremities than face
<b>Duration of process prior to epithelisation</b>	A year and more	3-6 months

	First Type	Second Type
Season of infection	Primary infection is possible throughout the year	Primary infection is possible only during summer and autumn months (July-October)
Epidemics	Rare	Heavy outbreaks develop easily
Virus reservoirs	Man	Wild desert rodents
Areas of distribution	Predominantly urban	Rural communities, city suburbs, desert areas
Number of parasites in lesions	Great	Small
Virulence for white mice	Low	High
Cross-immunity	Recovery from this type of cutaneous leishmaniasis does not afford immunity against second type	Recovery from this type of cutaneous leishmaniasis does not afford immunity against first type
Pathogen	<i>L. tropica minor</i>	<i>L. tropica major</i>

### Diagnosis

We have already discussed clinical diagnosis. The only precise confirmation is the demonstration of the parasites in the laboratory.

The leishmania parasites are most easily discovered in intact tubercles, as their number in leishmaniasis of the first type is very great. In the presence of ulcerative decomposition specimens for examination are curettaged from the edge infiltrate.

Specimens for investigation must be taken either from the tubercle or from the infiltrative ridge around the ulcer, striving for a minimum amount of blood to appear. For this purpose the tubercle or the infiltrated area is compressed by the left forefinger or a forceps so that as much blood as possible is pressed out (the area prepared for curettage must be completely cleared of blood). After this an incision is made with a scalpel and small bits of tissue are scraped off by means of this instrument from the walls or bottom of the incision; the present authors usually bite off a piece of tissue with an anatomic forceps. The tissue specimen together with the ichorous discharge is transferred to a glass slide where a smear is prepared and stained.

### Prognosis

In the overwhelming majority of cases the disease follows a cyclic course and is not very severe, and the patient is not incapacitated. However, the possibility of the development of more or less severe symptoms should also be considered: diffused infiltrates, edematous swellings, lymphangitis, secondary infections, etc. Crude interventions, such as burning or cutting out the sores, aggravate prognosis. The residual scars are usually smaller than the ulcers themselves, therefore the cosmetic defects are not great (Figs 49 and 50), with rare exceptions.





Fig. 49. Cutaneous leishmaniasis on face prior to treatment



Fig. 50. Same patient after treatment

### Immunity

One infection with cutaneous leishmaniasis does not provide any full guarantee against repeated infections. Upon recovery from cutaneous leishmaniasis only a relative immunity against the same type of infection is observed; this immunity is displayed by occasional absence of infection, or a noticeable decrease of the intensity of symptoms, number of ulcers, etc.

The period of morbidity is characterised by premunition, an immunity to superinfection (N. I. Latyshev, 1953).

### Prophylaxis

The prevention of cutaneous leishmaniasis can only be effected by extermination of sandflies (sprinkling DDT and hexachlorocyclohexane in living quarters, cattle sheds, stables, barns, outhouses, etc. Details are given in the chapter on pappataci fever).

A very effective prophylactic measure against cutaneous leishmaniasis in rural areas and semidesert zones is the extermination of rodents in populated communities and over a radius of 1-2 km from them.

Artificial inoculation with living cultures of *Leishmania* are administered for protection of people newly arrived in endemic localities; the cultures of pathogens of the type common to the given locality are employed. Usually the upper part of the thigh or shoulder are inoculated.

## Treatment

The extensive literature existing on cutaneous leishmaniasis is evident proof of the difficulty of the problem.

The list of old and new therapeutic measures is very long, but all of them are not very effective: the disease goes through a definite cycle and then the reverse process occurs. However, there exist some quite effective measures that give favourable results with proper management.

Currently there still does not exist any agent or method suitable for all stages and forms of leishmaniasis.

With the *first type of cutaneous leishmaniasis* the best results are obtained by treatment of the primary lesion in the first one or two months of its development. This tubercle can be removed either surgically or by diathermocoagulation; "destructive" salves or ointments containing antimony, arsenic, or pyrogallol may be applied for several days.

With small, clearly defined lesions the best results are obtained by injecting 5 per cent quinacrine around them. The poorest results with this type of treatment are attained when the tubercle is already 4-6 months old, i.e., when it is fully developed. Leishmaniasis sores that exist for a longer time than this period but have not decomposed and still possess more or less definite borders readily respond to quinacrine encircling injections, as they are thoroughly saturated with this drug. Ulcerating lesions are not indicated for quinacrine injections owing to the impossibility of attaining satisfactory saturation of the infiltrate with the quinacrine solution.

The technique of this method is very simple, but it calls for caution. Since quinacrine possesses an anesthetic effect there is no need of dissolving it in novocain. It is imperative to attain complete imbibition in the entire affected tissue and the area surrounding the lesion, as the parasites may be present external to the lesion. Small tubercles may be completely saturated by one injection.

The needle is inserted at a distance of 3 mm from the edge of the tubercle and moved into the skin towards its base (it must not enter the subcutaneous layers). The solution is injected under high pressure in order to attain complete saturation of the tubercle and of a surrounding 3-4 mm zone (the lesion is then surrounded by a bright-yellow "lemon crust" halo).

Single injections are insufficient when the tubercles are large, as the solution, injected under pressure, may spread out, leaving the affected area untouched. Several injections are required for large leishmaniasis lesions in order to attain complete and uniform saturation. The amount of quinacrine solution used in one injection ranges from 0.3 to 1-2 ml.

In certain cases, particularly when the lesions are small, single quinacrine injections are sufficient for cure: the crust falls away, the erythema disappears, and the tubercle gradually resolves, leaving an atrophic spot. In other cases complete reparation does not take place, or relapses may occur; this calls for repeated injections around the leishmanioma after



an interval of 2-3 weeks. Decomposition of the lesion is retarded by the application of 3 per cent potassium permanganate, officinal solution of ferric chloride or a 10 per cent solution of chloroform in 5 per cent iodine. These agents are applied to the lesions 2-3 times a week. Older unbroken lesions or lesions only superficially decomposed, respond best to quinacrine injections. Ulcerative lesions of the first type are treated with one of the following disinfectant ointments: 5-10 per cent protargol, 1 per cent quinacrine, 1 per cent rivanol, 10 per cent streptocide, Vishnevsky ointment, etc. It is not advisable to forcibly remove crusts that may form over ulcers.

In the *second type of cutaneous leishmaniasis* ulceration occurs so rapidly that it is not possible to curtail the process. Saturation of the infiltrate with quinacrine only results in the solution emerging from the ulcer. Besides, sometimes the large number of lesions (more than 30-40) limits the application of quinacrine.

In so far as the second type of leishmaniasis is associated with the formation of extensive ulcers and secondary infection local therapy with disinfecting ointments is applied. Dressings with these ointments may be changed every 2-3 days. It is recommended to alternate ointment dressings with moist dressings, occasionally with dusting powders. For complications of the erysipelatosus or acute inflammatory lymphangitis types penicillin injections are recommended. Nodular lymphangitis and resultant edema are treated by diathermy or exposure to sollux lamps (sunlight lamps).

Good results with diathermocoagulation are obtained in cases of small, chiefly non-ulcerative, lesions. The tubercle proper and the congested band around it (2-3 mm) are coagulated. Diathermocoagulation is of no avail for large ulcers.

Cryotherapy—freezing with carbon dioxide—produces positive effects on superficial leishmaniasis lesions.

### AMERICAN CUTANEOUS LEISHMANIASIS

Synonyms: Brazilian cutaneous leishmaniasis, leishmaniasis americana, espundia, mucocutaneous leishmaniasis, uta, South American leishmaniasis, Bahia ulcer, Bauri ulcer, chiclero ulcer, bosch yaws, forest yaws, nasopharyngeal leishmaniasis.

Pathogen: *Leishmania brasiliensis* (Vianna, 1922) (*L. tropica mexicana*, *L. tropica guianensis*).

### Geographical distribution

On the American continents the disease is prevailingly widespread in Mexico, Guatemala, Honduras, Peru, Bolivia, Paraguay, Venezuela, Guiana, Ecuador, Brazil, Uruguay, Colombia (important sites; reservoirs—dogs), North Argentina.

The disease was first classified in the 19th century in Brazil by Moreira (1825).

The epidemiological aspect has still to receive closer attention.

The vectors of this disease are *Ph. intermedius*, *Ph. panamensis*, and probably also ticks and horseflies (?). It is also considered that a tropical American rodent, the agouti, may harbour the infection.

The disease is widespread among people who work in forests, mostly among newcomers. Sporadic cases are observed in urban communities.

### Clinical aspects

The incubation period varies between 2-3 weeks and 2-3 months. Usually a slight eminence appears at first; an ulcer is formed at the top of this tubercle, then a crust. Lymphangitis is frequent.

In general the skin lesions are very like the Old World leishmaniasis sores. Several clinical varieties are differentiated: tubercular, non-disintegrating, ulcerative, eczematoid, papillomatous, and other forms.

The specific features characteristic of American leishmaniasis is the combination of skin lesions with lesions of the mucous membranes (in 20 per cent of patients). Mostly the nose, mouth, throat and vagina are involved in these mucosal lesions; they lead to extensive necrosis of the soft or even cartilaginous tissues that disfigure the patient. Local doctors term the disease "uta" when the process spreads from the skin to adjacent mucosa, and "espundia" when the skin and mucosal lesions are not adjacent. The duration of severe forms of the disease is 2-3 years, in rare instances of indolent courses and secondary infection amyloid degeneration of the organs and cachexia develop.

It has been pointed out long ago that Old World cutaneous leishmaniasis might involve the mucous membranes. Of recent years sufficient data has accumulated that confirms these observations. Thus in Central Asia the first type of the disease (since it mostly affects the face) has quite frequently been observed to manifest itself in a mucocutaneous form involving the mucosa of the nose, gums, eyes, etc. Analogous cases have been described in Spain, Italy, Ceylon, South Africa, and other countries. In these countries cases with either significant necrosis, or with deep lesions, or isolated involvement of the mucous membranes are much rarer. This has led certain authors to associate cutaneous leishmaniasis of the eastern and western hemispheres; however, it should be emphasised that a certain biological and clinical difference does exist between these two forms.

The mechanism of the involvement of the mucous membranes is not clear, particularly in cases where there is no direct (per continuitatem) transfer of the disease from the skin to the mucosa. Hence the assumptions of metastatic transfer of the *Leishmania* (Escomel). However, a most scrupulous examination of many hundreds of patients has not revealed the parasites in their blood. It should rather be assumed that the development of mucosal lesions is preceded by "mute" cutaneous leishmaniasis in the site of inoculation of the infection with subsequent diffusion per continuitatem along the lymphatics.

The theory that explains mucosal lesions by secondary fusospirillosis or blastomycosis infection is highly improbable.

## **Treatment**

Cutaneous forms are treated according to the principles expounded above for Old World cutaneous leishmaniasis. In cases of mucosal involvement it is recommended to combine usual treatment with prolonged administration of large doses of solusurmin (solustibosan) (as for visceral leishmaniasis).

A. E. Soland and V. M. Vargas (1960) obtained good results with pyrimethamine (chloridin, daraprim) prescribed for peroral administration in daily doses of 0.025-0.050 g in two ten-day courses; the interval between courses was 6-8 days.

### **SUDANESE (EGYPTIAN) CUTANEOUS LEISHMANIASIS**

There evidently exist several more clinical and epidemiological varieties of cutaneous leishmaniasis transmitted by various species of *Phlebotomus* flies; however, this matter requires a closer study (for instance, of late a form of cutaneous leishmaniasis has been described in Ethiopia, where the duration of the disease is as long as 3 years).

A definite variety is Sudanese cutaneous leishmaniasis. It is caused by *L. nilotica* (Brumpt, 1913) and possesses certain serologic features differing from *L. tropica major and minor*.

The clinical aspect of this form differs from that of other forms of leishmaniasis by the formation of keloid nodules that do not tend to ulcerate.

# TRYPANOSOMIASIS

---

Trypanosomiasis is any of several diseases due to infection with flagellate protozoans of the *Trypanosomidae* family. The two forms are African and American trypanosomiasis.

## AFRICAN TRYPANOSOMIASIS

Synonyms: trypanosomosis africana, morbus dormitivus (Lat.); sleeping sickness (Engl.); maladie du sommeil (Fr.).

The disease is characterised by irregular fever, skin rashes, enlarged lymph nodes, local edema, somnolence.

### Historical data

The first clinical description of the sleeping sickness was made by Atkins in 1724. From 1841 through 1890 various authors discovered in fish, frogs, mice, rats, and moles microscopic organisms which were united into the genus *Trypanosoma* (Gruby, 1843). In 1890, Neveu found trypanosomes in the blood of a patient suffering from the sleeping sickness; however, this investigator did not clarify the connection between the onset of the disease and the penetration into the body of these flagellate protozoans.

In 1901, Fordes and Dutton demonstrated and described *Trypanosoma gambiense* in human blood. Castellani (1902) found it in the spinal fluid of a sleeping sickness patient.

Bruce and Nabarro (1903) finally proved *T. gambiense* to be the cause of the sleeping sickness and established that its vector was the tsetse fly (*Glossina palpalis*). In 1909, Kleine made a study of the developmental cycle of *T. gambiense* in the tsetse fly.

Stephens and Fantham (1910) classified *Trypanosoma rhodesiense* as an independent species.

## Etiology

The causative agents of African trypanosomiasis are two closely related species of the genus *Trypanosoma*: *T. gambiense* (Dutton, 1902), and *T. rhodesiense* (Stephens a. Fantham, 1910). In human blood the two species are undifferentiable; only following inoculation into animal organisms does it become possible to discern certain morphologic differences; however, it is questioned by certain authors whether these differences constitute characteristics of distinct species.

When observed in fresh drops the trypanosomes are elongated, light, motile microscopic organisms. In blood smears stained with the Romanovsky stain the plasma of the trypanosome is pale blue, a red nucleus lies in its centre, and at one end there is a red blepharoplast from which extends a wavy flagellum. An undulating membrane is stretched between the flagellum and the body of the parasite. Locomotion is provided by oscillation of the flagellum and membrane, and likewise by undulation of the body itself. The length of a trypanosome is 15 to 40 microns, its width 1.4-2 microns (Fig. 51).

Two forms of *T. gambiense* are differentiated: the long, narrow form (30-40 microns long), possessing flagella much longer than the body, and the short, wide form with flagella the length of which does not exceed the anterior end of the body; a number of transitory forms are also observed.

## Epidemiology

The source of infection is man, wild and certain domestic animals (antelopes, sheep). African trypanosomiasis is a disease with natural foci; however, the principal source of infection is most probably man. The

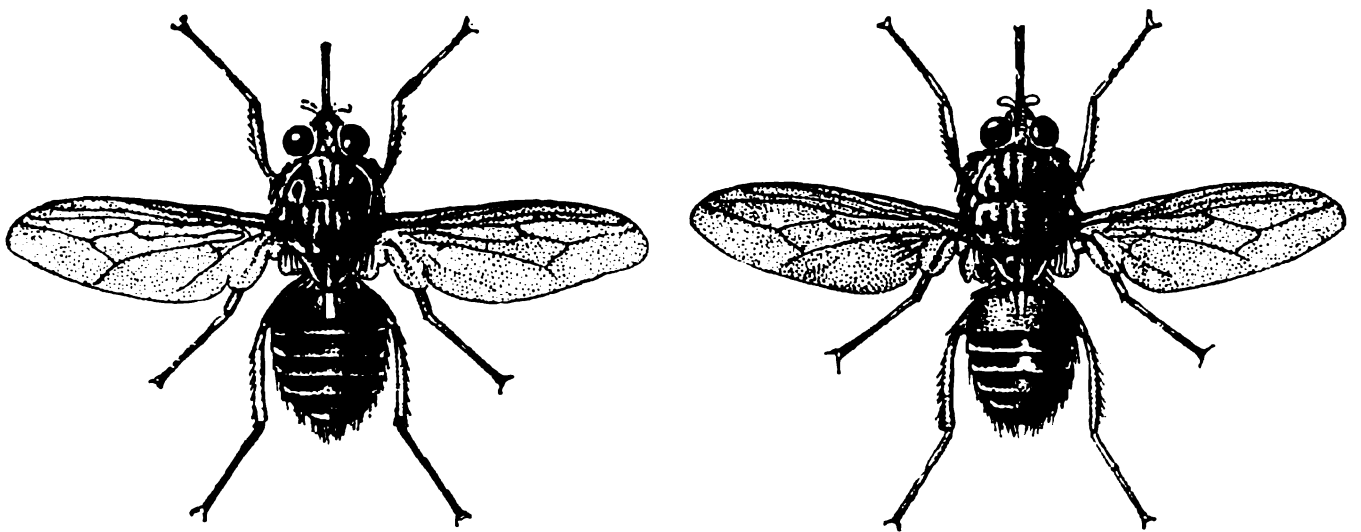


Fig. 52. Tsetse flies — vectors of African trypanosomiasis (Manson-Bahr) *Glossina palpalis*; *Glossina morsitans*

vectors of *T. gambiense* are the bloodsucking tsetse flies (Fig. 52) *Glossina palpalis*, *G. tachinoides*, *G. morsitans*, *G. longipalpis*, *G. swynnertoni*, and other species. The vectors of *T. rhodesiense* are *G. morsitans* and *G. swynner-*

*toni*. The infection is transmitted by both the females and the males, but the former are more aggressive than the latter.

The *Glossina* flies become infested by ingesting the blood of infected men and animals. The developmental cycle of the trypanosomes in the body of the insect takes 12 to 20 days, the parasite ending up in the salivary glands of the fly. As soon as this occurs the tsetse fly becomes infestive, transmitting the parasites with its saliva into man and animals when it bites through their skin to obtain blood. Direct man-to-man transmission is also possible via blood transfusion, contaminated hypodermic needles and needles used for obtaining blood specimens.

**Geographical distribution**

Sites of the disease evoked by *T. gambiense* are located in Africa—in the Republic of Congo, Gambia, Sierra Leone, Ghana, Nigeria, Cameroon, Southern Sudan, Uganda; the highest incidence of the disease is observed among the people living on the banks of the Congo river and its tributaries.

The form of trypanosomiasis caused by *T. rhodensiense* is widespread in north-eastern Africa, south and west of Nyasa lake (Fig. 53).

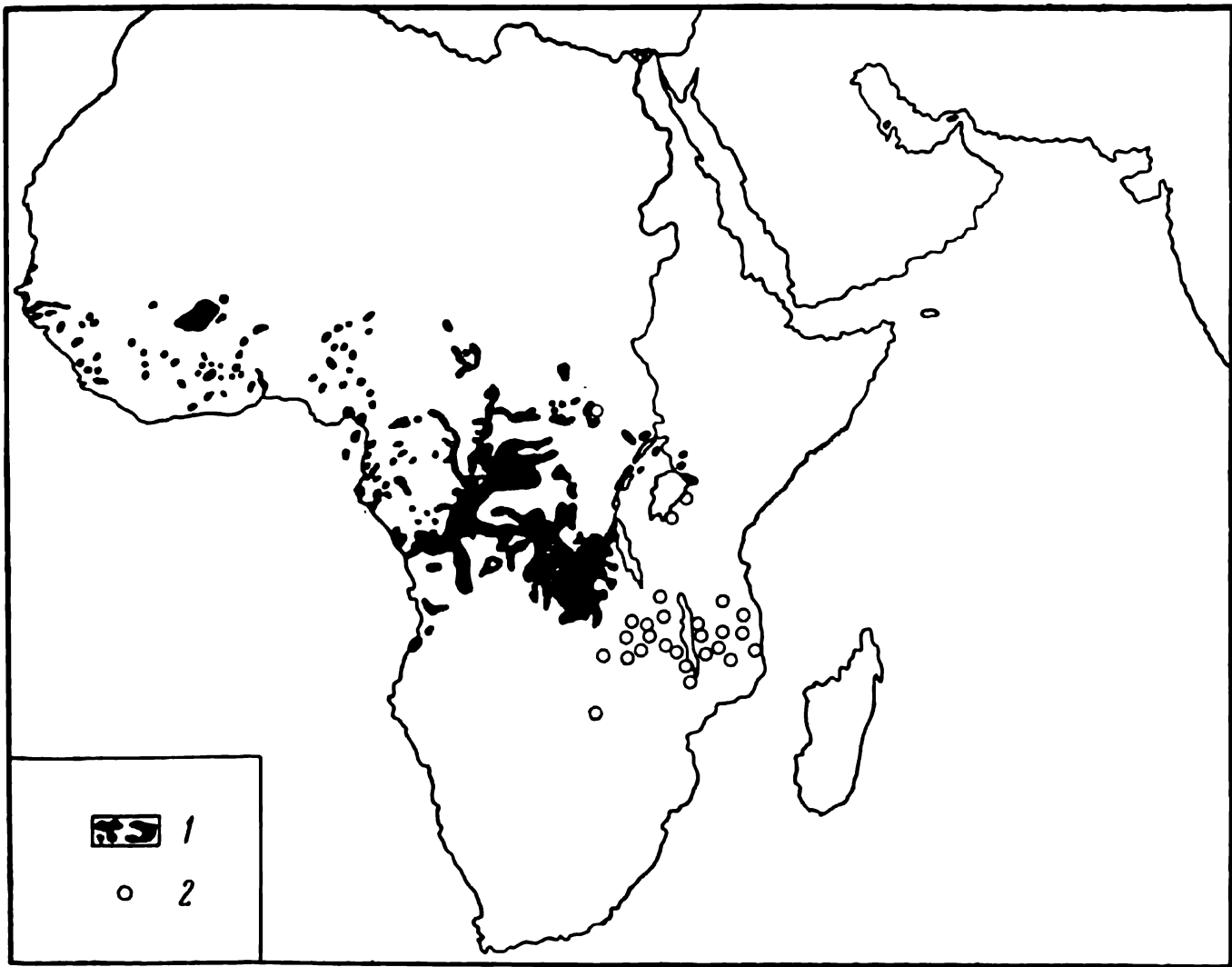


Fig. 53. Geographical distribution of African trypanosomiasis  
1 — *Trypanosoma gambiense*; 2 — *Trypanosoma rhodensiense*

## Clinical aspects

The incubation period, as ascertained by exposing animals to bites of tsetse flies and by direct injection of trypanosomes, is 2-3 weeks. Observations of human beings showed it to be two weeks. A. Y. Raskin (1935) has described a case of infection with *T. gambiense* contracted in the laboratory through a prick with a pipette containing infected blood; the incubation period in this instance was 8 days.

The parasites are demonstrable in thick films 3 weeks after inoculation; with more sensitive techniques — examination of centrifuged citrate blood — they may be discovered earlier.

The so-called trypanosome chancre — a blister with a diameter of 1-2 cm surrounded by a whitish waxy zone — is formed at the site of inoculation (the bite of the fly); this blister disappears within several days.

Trypanosomiasis is accompanied by an irregular temperature. Elevations may be moderate, but sometimes the fever jumps to 41°C. The pyrexial periods go on for weeks, interspersed with remissions lasting for days or weeks.

Erythematous circinate eruptions, 15 cm and more across, appear on the skin. These eruptions are localised for the most part on the chest and spine, but they may involve the face and other parts of the body as well. In some cases a nodular erythema is observed. Frequently an intensely itching papular rash appears. Swellings are noticeable on the face, hands, feet, and in the sites of the erythematous eruptions.

A characteristic feature is the enlargement of the peripheral and mesenteric lymph nodes. Particularly noticeable are the enlarged cervical lymph nodes in the triangle at the back of the neck; at times they grow to the size of a pigeon's egg. These enlargements are at first soft, then they become indurated.

Cardiovascular involvement is manifested by tachycardia.

The spleen and liver are frequently enlarged. Nervous symptoms: insomnia and hyperesthesia that makes even a slight touch very painful.

Iridocyclitis and choroiditis have been observed. Some male patients complain of impotency, females — of miscarriages, amenorrhea, sterility. The general weakness gradually intensifies, mental and physical debility increase, anemia appears.

The severity of the described clinical signs and symptoms and the duration of the period of the disease varies greatly in different patients. Seemingly healthy parasite carriers and blurred forms have been described as well as very severe cases of the disease. In the absence of treatment the patients usually succumb to secondary diseases or to status epilepticus and coma. In the majority of cases the disease passes into its second — terminal — phase, known as the sleeping sickness in the narrow sense of this term.\*

---

\* The herein described sleeping sickness has nothing in common with lethargic encephalitis.

This transition occurs gradually, sometimes it takes several years from the moment of inoculation.

The most characteristic feature of the second period is the increasing somnolence. This condition is usually apparent in the daytime, while at night sleep is often disturbed. The patient drags his feet as he walks, his facial expression becomes sullen, the lower lip hangs down and saliva dri- vels over it, he loses all interest in his surroundings, answers questions slowly and reluctantly, complains of headache. Tremors of the tongue, hands, and feet appear, and also fibrillary muscular tremor.

The somnolence gradually increases, the patient falls asleep even while taking food, his sleep becomes so deep that it is, according to Kellersberger and Bercovitz (1944), "similar to death". The tremor intensifies, at times convulsions occur, and then paralysis. In some cases rigidity of the neck is observed, ptosis of the eyelids, edema of the optic disk.

The duration of this period of the disease is approximately 4-8 months, frequently less, but occasionally about one year. The patients succumb to cachexia associated with coma or to secondary diseases.

Such is the clinical aspect of trypanosomiasis caused by *T. gambiense*. The clinical picture of the *T. rhodesiense* infection is in general the same, but the disease takes a more acute course. The pyrexial periods are longer, the apyrexial periods shorter, symptoms of central nervous system involvement appear earlier (weakness, emaciation). Death is usually sudden, before the second period of the disease has set in. The total duration of the disease is about one year in the absence of treatment; according to Willet (1955) it is from 3 to 9 months in typical cases.

In certain areas of Africa trypanosomiasis is a truly national calamity.

### Diagnosis

Clinical findings must be substantiated by diagnostic examinations of the blood, lymph, and cerebrospinal fluid for trypanosomes.

Blood specimens are examined in thick films treated with Romanov-sky's stain. However, the number of trypanosomes in the blood is fre- quently very small, and therefore the method of accumulation is resorted to. The technique is as follows: 1 ml of 3 per cent sodium citrate\* and 9 ml of venous blood are drawn into a 10 ml syringe.

This mixture is centrifuged for 10 minutes at 1,000-1,500 rev/min. The upper layer of the sediment is examined for living trypanosomes, or a smear is prepared with this layer and then stained with the Romanovsky's stain. If the result is negative the liquid over the sediment is transferred to another test tube, centrifuged for 20 minutes, and the resultant sedi- ment is again examined.

The lymph node punctures should be done at early stages of the dis- ease, while the nodes are still soft and full. The lymph specimens are

---

\* Manson-Bahr (1954) recommends 1 ml of 6 per cent sodium citrate in an 0.9 per cent solution of sodium chloride.



examined in smears stained after Romanovsky, or the living parasites are looked for in native preparations. In the latter case the examination should be conducted in dimmed illumination, with a lowered condenser, or in a dark field.

Analysis of the cerebrospinal fluid shows an increased protein content and increased number of blood elements (owing to lymphocytosis), and occasionally the presence of trypanosomes. This examination is employed not only as a diagnostic aid, but also in order to check the efficiency of the treatment and the selection of therapeutic tactics.

### **Pathology**

Central nervous system lesions include chronic leptomeningitis, cerebral edema, thickening of the cerebral convolutions, occasionally hemorrhages. The ventricles of the brain are distended by the fluid they include; the blood vessels are constricted, while their walls are thickened. The parasites emerge from the bloodstream into the brain tissue, accumulating chiefly in the frontal lobes, the pons, and medulla oblongata.

### **Treatment**

A number of agents are used in the treatment of trypanosomiasis; Antrypol, tryparsamide and pentamidine-isethionate are most frequently employed.

*Antrypol* (suramin, Bayer 205, germanin, Fournau 309, moranyl, naganol) is a preparation of urea, effective in the early phases of the disease, while the trypanosomes have not yet penetrated into the central nervous system. It is usually injected intravenously, less frequently intramuscularly, in a 10 per cent solution. The initial dose is 0.3-0.5 g, subsequent single doses contain 1 g; sometimes the latter doses are increased to 1.5-2 g (Manson-Bahr, 1954). The total dosage for a course of treatment is approximately 10 g. Injections are repeated at weekly intervals.

If necessary a second course of treatment is commenced one month after the termination of the first. Occasional side effects are albuminuria, skin eruptions, infrequently neuritis.

*Tryparsamide* (tryparsone, Fournau 270 [orsanine], tryponarsyl, trypotan, novatoxyl, glyphenarsine) is a preparation containing 25.1 per cent arsenic. It is particularly effective for lesions of the central nervous system. Tryparsamide is given intravenously or intramuscularly, as a 10-20 per cent solution in distilled water. A single dose is 1-4 g (the maximum permissible single dose is 60 mg per kg of body weight). The ordinary procedure is to inject 1 g of the preparation initially, while subsequent injections given three times a week contain 2 g each. The total dosage for one course is 15-30 g. In cases of involvement of the central nervous system a second course of treatment is prescribed one to three months after the first.

The severest, and, happily, rarest, side effect evoked by tryparsamide is neuritis of the optic nerve. Administration of the preparation is discontinued upon the very first signs of this complication manifested by photophobia, pain in the eyes and loss of visual acuity. Unfortunately, the symptoms of neuritis sometimes appear only after the entire course of treatment with arsenic preparations has been completed. Arsenic dermatitis and exacerbation of a specific process in the organs may also appear.

*Arsobal* (Mel B) is a pentavalent arsenical preparation insoluble in water. It is administered only intravenously in a 3.6 per cent solution in propylene glycol.

Arsobal therapy is mostly resorted to in advanced stages of the disease. Apted (1957) recommends a course of treatment that includes three-day cycles over intervals of one week. On each day of treatment one arsobal injection is made; the dose for each injection is 1.8-3.6 mg/kg.

#### Plan for treatment of patients weighing 50 kg.

*First cycle.* For three consecutive days the patient is injected with daily doses of 2.5 ml arsobal solution (1.8 mg of the preparation per kg of body weight).

One week interval

*Second cycle.* First day: injection with 3 ml of arsobal solution (2.16 mg of preparation per kg of body weight). Second day: 4 ml of arsobal solution (2.88 mg/kg). Third day: 5 ml of arsobal solution (3.6 mg/kg).

One week interval.

*Third cycle.* For three consecutive days the patient is injected with daily doses of 5 ml of arsobal solution (3.6 mg/kg).

Taube and Nixon (1958) prefer two 4-day cycles of treatment with 10- to 14-day intervals between cycles. On the days of treatment they administer from 2 to 3.6 mg of the preparation per kg of body weight in one injection.

*Mel W* is a water-soluble derivative of arsobal. It is used as a 5 per cent solution prepared either in normal saline solution or in 5 per cent glucose. Injection is intramuscular or subcutaneous in increasing doses from 1 to 5 mg of the preparation per kg of body weight daily (but not exceeding an absolute dose of 200 mg) for four consecutive days; after a one-week interval the cycle of injections is repeated (Friedheim and Jongh, 1959).

In some instances the trypanosomes have been observed to possess a resistance against arsenicals. This is evidently not a primary immunity of the protozoans, but one that has been acquired as the result of inadequate treatment in the past either of the given patient himself, or of the patients from whom he received the trypanosomes via the tsetse flies.

*Pentamidine-isethionate* is an aromatic diamine compound. It is effective only in the early phases of the disease. Administration is predominantly intramuscular, less frequently intravenous.

The dosage for intramuscular injection is 0.004 g/kg, for intravenous injection 0.002-0.004 g/kg. For intramuscular injection the preparation is dissolved in 3 ml of distilled water, for intravenous—in 5 to 10 ml of distilled water. The injections are performed daily or on alternate days, their total number is 8-10. Intravenous injections occasionally evoke a drop

in arterial pressure, therefore they should be performed very slowly, over a period of 3-5 minutes. A dose of 0.25 ml of a 1 : 1,000 solution of adrenalin is injected directly before the pentamidine-isethionate injection in cases when the patient's arterial pressure was previously observed to fall following the injection of this preparation. Some authors prefer to treat trypanosomiasis with a consecutive prescription of different preparations, e.g., three injections of 1 g of antrypol over five-day intervals, and then 3-5 injections of 2 g of tryparsamide over similar intervals. Such combinations are particularly recommended for infections caused by *T. rhodesiense*.

Trypanosomiasis treatment should be checked by examination of the spinal fluid; the increase in this fluid of protein and of cellular elements obligates the administration of repeated courses of tryparsamide treatment. Out-patient observation of these cases is continued for 2 years, spinal punctures are done every 3-6 months.

### Prophylaxis

Measures employed for controlling trypanosomiasis include a planned check-up and treatment of patients and parasite-carriers and their isolation in places inaccessible to the tsetse flies, protection against tsetse bites by nets over doors and windows, the employment of insectifuges (dimethyl phthalate and other agents), and the wearing of white clothing.

For extermination of the flies living quarters are treated with DDT and other insecticides. In forests umbrellas or towels are covered with sticky substances and these improvised fly-catchers are carried across clearings; the flies are attracted by the moving object and are thus caught in multitudes.

Some authors have proposed to exterminate the antelopes that are the reservoir of the infection; however, this measure might cause economic losses and would not solve the problem anyhow, as man himself and certain domestic animals are also reservoirs of the infection.

Chemoprophylaxis is also employed; healthy persons are injected with antrypol or pentamidine-isethionate. Fourché has reported that the intravenous injection of 1 g of antrypol affords protection for six months; according to other authors this immunity is valid for only six weeks. Prophylactic injections of pentamidine-isethionate for adults contain 0.004-0.005 g of the drug per kg of body weight.

### AMERICAN TRYPANOSOMIASIS

Synonyms: barbiero fever, Brazilian trypanosomiasis, Chagas' disease, South American trypanosomiasis. The disease follows either an acute or a chronic course. The first form is observed predominantly in children and is characterised by high fever, enlargement of the lymph nodes, liver and spleen, a frequent appearance of a primary lesion on the skin or the

conjunctiva, occasionally by severe heart trouble and involvement of the central nervous system. The chronic form evokes various degrees of myocardial lesions.

### Historical data

In 1907, Chagas discovered trypanosomes in the intestine of the assassin (reduviid) bug *Panstrongylus megistus* (*Triatoma megista*). In 1909, this author described human trypanosomiasis in South America caused by a trypanosome analogous to the one previously found in the assassin bug.

### Etiology

The pathogen of American trypanosomiasis *Trypanosoma* (*Schizotripanum*) *cruzi* (Chagas, 1909) attains a length of 15-20 microns in the blood.

A characteristic feature of the trypanosome is that it penetrates into the cells of various organs and tissues (the heart musculature, the skeletal muscles, the central nervous system, the adrenal glands, etc.). The parasites

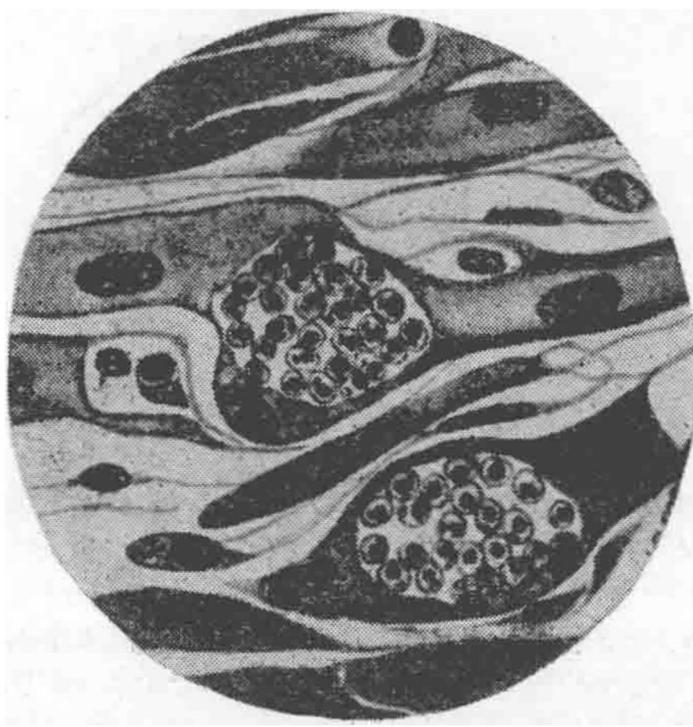


Fig. 54. *Trypanosoma cruzi*.  
Schizogony in myocardium  
(preparation by Gordon-  
Thomas)

multiply in these cells, taking on a leishmanial shape (round formations with no flagella). After a certain period of time these leishmanial forms turn into crithidial forms (an elongated body with a flagellum projecting from its middle and a rudimentary undulating membrane) that develop into trypanosomes which then emerge into the blood (Fig. 54).

In Central and South America two more species of trypanosomes have been discovered in human blood; they are *Trypanosoma rangeli* (Tejera, 1920), and *T. ariarii* (Renjito a. Uribe, 1951).

## Epidemiology

The vectors of the trypanosomes are bugs of the family *Reduviidae*: *Panstrongylus* (*Triatoma*) *megistus*, *Triatoma infestans*, *Rhodnius prolixus*, *Eratyrus cuspidatus*, and other species.

One of the principal vectors *Panstrongylus megistus* (Fig. 55), the assassin or cone-nose bug, has also received the name of “kissing bug” as it attacks sleeping people and commonly bites them in the lips at the margin between the skin and mucosa.

The infection is transmitted by adult winged bugs, and by their larvae and nymphs. They ingest the trypanosomes with the blood of infected

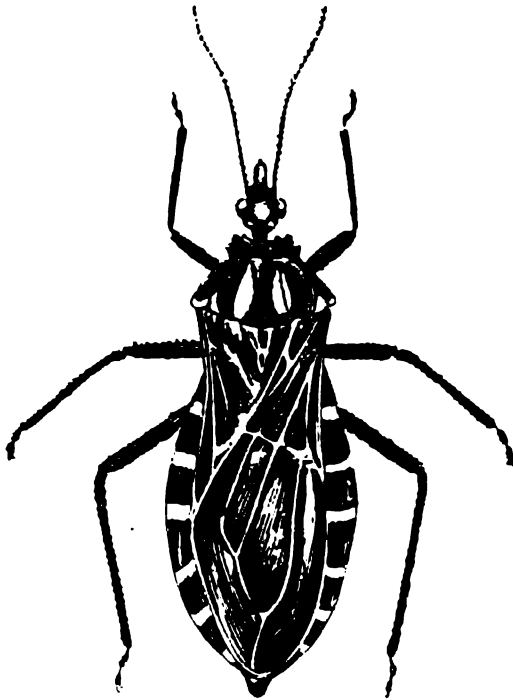


Fig. 55. *Panstrongylus megistus*, vector of American trypanosomiasis (Chagas)

humans or animals. In the gut of the bug the trypanosomes multiply and develop within 8-10 days and are then defecated. When such trypanosomic fecalia contaminate the site of the bug's bite, or any other lesion on the skin, the parasites penetrate into the human or animal body. Sometimes the site of access is the conjunctiva of the eye. Herbig-Sandreuter (1955) holds that *T. rangeli* may likewise be transmitted by the bite of the bug, as the parasites are also found in its salivary glands. American trypanosomiasis has also been transmitted through blood transfusions.

American trypanosomiasis is a natural endemic disease. Besides man, a number of wild and domestic animals are hosts of the infection: armadillos, opossums, rodents, monkeys, dogs, cats, etc.

## Geographical distribution

Sites of the disease have been registered in Brazil, Venezuela, Western Argentina, Panama, Guatemala, Bolivia, Peru, Ecuador, Chile, Salvador, Uruguay, Colombia, Mexico (Fig. 56).

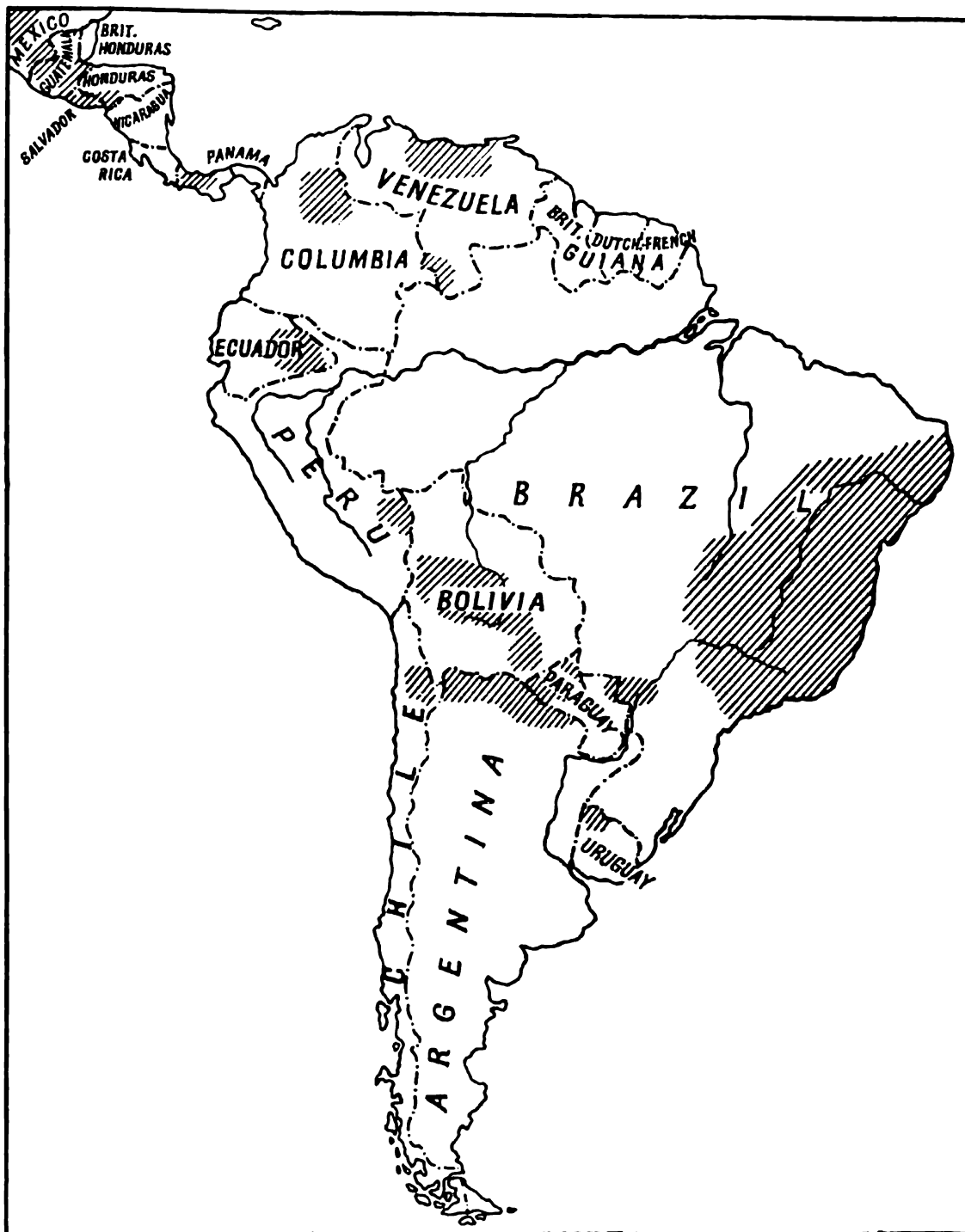


Fig. 56. Geographical distribution of American trypanosomiasis (Chagas' disease)

### Clinical aspects

Two forms of the disease are distinguished — the acute and chronic forms. The acute form begins after an incubation period of 7-14 days with indisposition, chills, headache, muscular pains; often a basic lesion, or chagoma, appears at the site of inoculation of the infection; this is an inflammatory infiltrate with lymphangitis and enlargement of the regional lymph nodes. Outwardly the chagoma resembles a furuncle, but it never festers. Mazza and his co-workers have described secondary chagomas — nodules in the subcutaneous tissues formed as a result of hematogenous dissemination of the trypanosomes. These are hard nodules firmly adhering to the skin; the latter becomes purplish-red over the nodules or retains its normal aspect. Penetration of the trypanosomes through the conjunctiva

causes uni- or bilateral conjunctivitis and edema of the eyelids (Romaña's sign); this is at times accompanied by dacryocystitis and often by puffiness of the face. In some cases fine red macular eruptions of pin-head size appear on the chest; they persist for 8-10 days.

The cervical, inguinal and axillary lymph nodes become enlarged. Generalised elastic edema appears in many cases, particularly noticeable on the outer aspect of the feet, on the thighs, and on the face. According to current opinion, the pathogenesis of these edemas is based on hypoproteinemia, particularly the lowered concentration of albumins in the plasm (Laranja et al, 1948).

American trypanosomiasis is accompanied by either constant or remittent fever, the peaks attaining 39-40°.

Cardiovascular symptoms include extension of the cardiac margin, at times a galloping rhythm, occasionally pericardial exudation; electrocardiography shows a longer *P-R* interval, and changes in the *QRS* complex, the *T* peak, ventricular extrasystole, symptoms of right bundle-branch heart block. The liver and spleen are enlarged. Romaña (1953), Hartz and Toledano (1954) observed several cases of the onset of specific orchiepididymitis and parotitis. The blood shows leukocytosis with monocytosis; a leukemoid reaction of the lymphocytic type has been described.

In the terminal phase of the disease meningoencephalitis is often observed; its appearance is a bad prognostic sign. Patients usually succumb with symptoms of heart failure. In favourable courses of the disease the temperature returns to normal within 4-5 weeks, the trypanosomes disappear from the peripheral blood, the general state of the patient gradually improves, and the disease passes into a chronic condition.

Laranja et al. differentiate the following varieties of the chronic form of the disease: the indefinite form (potential cardiopathy), the cardiac form (chronic cardiopathy), and the nervous (?) form. They themselves have not had occasion to observe the latter form and therefore they doubt the value of classifying this form separately.

Patients affected with the indefinite form of the infection show no signs of the disease for the time being; however, the trypanosomes are retained in their bodies and may with time involve the heart to such a degree that the lesion is manifested by clinical symptoms. Patients affected with chronic cardiopathy complain of indefinite pains in the area of the heart and the upper part of the abdomen, short breath, heart palpitations. Percussion shows the heart to be extended, auscultation establishes impaired rhythm, splitting of the second heart sound over the pulmonary artery, occasionally a galloping rhythm. In some cases myocardial involvement is only established by electrocardiography. The patients usually die before fifty; they succumb to chronic heart failure, sometimes passing away suddenly owing to acute heart attacks.

The nervous form of chronic trypanosomiasis described by certain authors (Chagas, 1934-36, and others) is characterised by convulsions; occasionally paralysis may occur.

Changes in the thyroid glands are frequently observed in trypanosomiasis patients, but the connection of these changes with the trypanosome invasion is very doubtful, and they are evidently symptoms of endemic goiter. Goble (1954) infected dogs with trypanosomiasis and found no thyroid disturbances in the experimental animals. Another noteworthy point is the incidence of asymptomatic and mild forms of the disease that clear up spontaneously.

Thus, in Guatemala 3 per cent of the infant population younger than five months is infected with trypanosomiasis; the parasites are found in the blood for a period of 10 to 30 days. Asymptomatic parasite-carriers are often found among adults.

Experimental trypanosomiasis produced in adult cases of progressive paralysis and malignant tumours is frequently quite mild and terminates in spontaneous recovery.

### Diagnosis

For establishing differential diagnosis it is first necessary to exclude leishmaniasis and malaria; this is easily done by comparing clinical and laboratory findings. For instance, hepatosplenomegaly due to trypanosomiasis never attains the degrees common to visceral leishmaniasis. The absence of *Leishmania* parasites in bone marrow specimens obtained by sternal puncture is concluding evidence against the diagnosis of leishmaniasis. Repeated negative tests of the blood for malaria plasmodia repudiate this diagnosis, too.

Laboratory tests for trypanosomes are done by examining blood and spinal fluid specimens; however, the parasites are sometimes found with difficulty, particularly in chronic forms of the disease. Therefore the method of xenodiagnosis is resorted to. For this purpose a guinea pig is injected with 5-10 ml of the patient's blood and two weeks later the blood of the animal and its visceral organs are examined for trypanosomes; another method is to feed the patient's blood to vector bugs bred in the laboratory and then to examine the guts of these insects for the trypanosomes. The complement-fixation test is also employed; in it the antigen substance is an extract prepared from the heart and spleen of infested animals.

### Pathology

Post-mortem findings show myocarditis and the presence of the parasites in the muscular fibres; infiltrates containing lymphocytes, monocytes, and plasmacytes are visible between the fibres; pericarditis and endocarditis are sometimes observed. The dura mater is hyperemic and adheres to the skull bones, the pia mater is thickened and edematous, a gelatinous exudate is present in the subarachnoid space, small hemorrhages are visible in the brain and spinal cord, sites of infiltration of polymorphonuclear leukocytes are situated near the nerve cells invaded by the trypanosomes.



The adrenals show inflammatory reactions to the penetration of the parasites into the cells of the cortical and cerebral layers. In the liver there is hyperemia and fatty degeneration of the cells. Myositis is present in the skeletal muscles, particularly in the extremities.

### **Treatment**

American trypanosomiasis is treated with the quinoline derivative Bayer 7602 and with arseno-phene-sulfate-Bayer 9736.

Bayer 7602 is injected intramuscularly in 3 per cent aqueous solutions either every day or every other day; single doses are gradually increased from 3 to 20 ml of the solution. The total dosage for a course of treatment for adults is 30-60 mg/kg.

Bayer 9736 is less toxic, but it is also less effective than Bayer 7602. The preparation 9736 is injected intravenously 2-3 times a week in 10 per cent solution; initial doses are 1.5 ml, gradually increasing to 3-4.5 ml. The maximum total dose for adult males is 50 ml of solution (5 g of the preparation); for adult females it is 40 ml of solution (4 g of the preparation); children are not given more than 30 ml (3 g of the preparation).

Laranja and his co-workers (1948), using large doses of penicillin (500,000 u every 3 hours for 10 days) obtained contradictory results: in some patients excellent results were obtained, in others the treatment proved unsuccessful. Certain other authors reported failures with antibiotics (penicillin, streptomycin, chloramphenicol, aureomycin, erythromycin, etc.).

### **Prophylaxis**

Prophylaxis is conducted by exterminating the *reduviid* vectors with DDT and other insecticides.

# TICK-BORNE RELAPSING FEVERS

---

Synonyms: tick-borne spirochetosis, tick-bite relapsing fever, tick-borne relapsing typhus, tick-bite recurrence (in Soviet terminology); recurrent fever, relapsing fever, tick fever, tick-borne relapsing fever, famine fever, remittent fever, spirillum fever (Engl.); fièvre récurrente à tiques (Fr.); Zeckenrückfallfieber (Germ.). There are also a number of various local names: Central Asian, Persian, North African relapsing fever, etc.

## HISTORICAL DATA

In 1873, Obermeier published a work in which he reported the discovery of spirochetes in the blood of relapsing fever patients. Shortly after the appearance of Obermeier's work G. N. Minkh, a physician in the Odessa Hospital of Infectious Diseases, injected himself with the blood of a relapsing fever patient (by means of a glass capillary pipette) and in six days he was down with this disease (1874). At that time Minkh expressed his opinion that the pathogens of both relapsing fever and classic epidemic typhus were transmitted by parasitic insects that lived on human blood. He wrote of this in an open letter to the editor of the journal *Letopis Vrachebnaya* (*Medical Chronicles*) (Feb. 2, 1878).

The role of ticks in transmitting Asiatic relapsing fever was first marked by Russian explorers and physicians.

In 1913 Y. Junkovsky investigated a number of cases of fevers associated with tick bites; he found spirochetes in the blood smears, and therefore concluded that the patients were afflicted with a tick-borne relapsing fever caused in Persia by the bites of domestic ticks. This author classified the causative agent of the disease—the spirochete—as an independent species standing apart from the pathogen of louse-bite spirillum fever and closely related to that of African spirillum fever. Y. I. Martzinovsky (1921) observed a number of cases of Persian relapsing fever among Russian soldiers stationed in Kasvin and Hamadan (Iran).

The first report on the existence of tick-borne relapsing fever in Central Asia was made by V. I. Magnitsky, an army doctor who established a case

of this disease in a colleague of his, Dr. Aronson, who had recently arrived from Eastern Bokhara.

N. I. Latyshev was the first researcher who tried to find the vector of relapsing fever in Central Asia (Tashkent) by experiment; this experiment he conducted on himself, exposing an arm to the bites of *Ornithodoros* ticks taken from premises in which there had been a case of relapsing fever. On April 25, 1926, he thus fed eight ticks, and another five three days later. On May 8, Latyshev fell ill with relapsing fever. In Leningrad (a non-endemic zone) I. A. Moskvina artificially infected, for therapeutic purposes, three progressive paralysis patients through the agency of *Ornithodoros papillipes* ticks.

Subsequently many authors made comprehensive descriptions of the clinical findings and epidemiology of tick-borne relapsing fever. The contributions of Y. N. Pavlovsky and his co-workers in the development of the entire teachings on tick-borne relapsing fever, its vectors and pathogens were of signal importance.

Among the researchers of other countries who were most active in furthering knowledge on spirochete fever are Nicolle, Manson, Brumpt, Nuttal, and Wenyon.

### THE CAUSATIVE AGENT

Formerly the pathogens of various forms of tick-borne relapsing fever were designated as belonging to the genus *Spirochaeta*, which is now called *Borrelia*. The morphological structure of the various species of spirochetes is in general similar; the slight differences in the forms of the coils or contours of the spirochetes, considered by some authors to be characteristic of one or another species, actually depend on the technique employed in preparing smears, on the time when the specimen is taken, on the age of the spirochetes, and on the biological properties of the vector.

The spirochete is an elongated, slightly corkscrew-like spiral filament; occasionally it is seen in the form of a crescent. Mature individuals are 15 to 25 microns long and 0.25 microns wide. Both ends of the spirochete are pointed. The younger forms are one-and-a-half times shorter and somewhat thinner.

The number of coils or bends varies from 3 to 6, on the average 4 (Fig. 57).

The spirochete multiplies by transverse fission.

The species of spirochetes differ in their biological properties, in their adaptation to different species of ticks, and likewise in the susceptibility of various laboratory animals to them. The formation of distinct geographic strains of spirochetes is connected with these features.

### EPIDEMIOLOGY

The vectors of the spirochetes that cause tick-borne relapsing fever are *Ornithodoros* ticks of the family *Argasidae*, subfamily *Ornithodorinae*, class *Arachnoidea*, phylum *Arthropoda*. Global fauna currently lists 64

species and varieties of ticks of the subfamily *Ornithodorinae*. Three of these species and varieties are common to the Soviet Union and 61 to foreign lands. The northern limits of *Ornithodorinae* habitats in both hemispheres run along 50° N. lat. Tick-borne relapsing fever is widespread in areas south of the July isotherm, that is 24-25° (only in North America is it somewhat more northerly); in the southern hemisphere the line is north of the January isotherm, which is also 25°.

A hungry tick is dark-grey; after it has had its fill of blood it becomes dark-red or dark-brown. Satiated females are 12 mm long, 10 mm wide, and 7 mm thick. Males and hungry females are approximately 2 times smaller; the decrease is particularly noticeable in the thickness of the tick.

The body of the tick is covered with a chitin case; the dorsal surface is rough, resembling shagreen (Fig. 58 *a* and *b*).

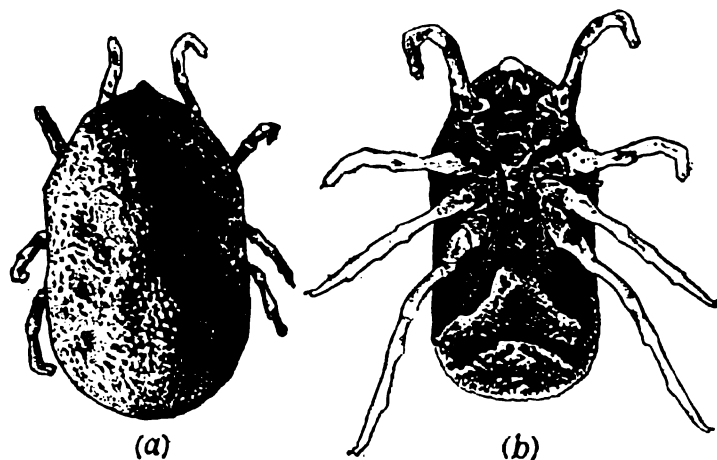


Fig. 58. *Ornithodoros* tick, spirochete carrier  
*a* – back; *b* – abdomen

Tick-borne relapsing fever is an endemic disease with natural foci widespread among wild vertebrate animals.

There exist natural and settlement endemic sites of relapsing fever. In natural sites the vector-ticks live in natural shelters—burrows, rock-cracks, caves; in settlement sites they inhabit old adobe buildings and masonry, animal sheds, pens, sties, barns. In natural foci man contracts the infection only when he goes to localities inhabited by infested ticks (in Eastern lands relapsing fever is also called “travellers’ disease”) (Figs 59 and 60).

Settlement endemic sites are very dangerous sources of infection, as the ticks live in close proximity to man.

The ticks bite men and animals both during the day (they are not afraid of diffused light, but run away from direct sunlight) and at night. The female lays its 0.8 mm ova in piles of 40-50 eggs.

At the end of the second week the ovum breaks open and the larva emerges.

*Ornithodoros* ticks attack various wild and domestic animals and man.

Transmission of the spirochetes: after the tick has punctured the skin it extracts blood (bloodsucking may continue for half an hour). From the infested animal (either diseased or a parasite-carrier) the spirochetes



Fig. 59. Y. N. Pavlovsky showing local inhabitants ticks in dust in their courtyard

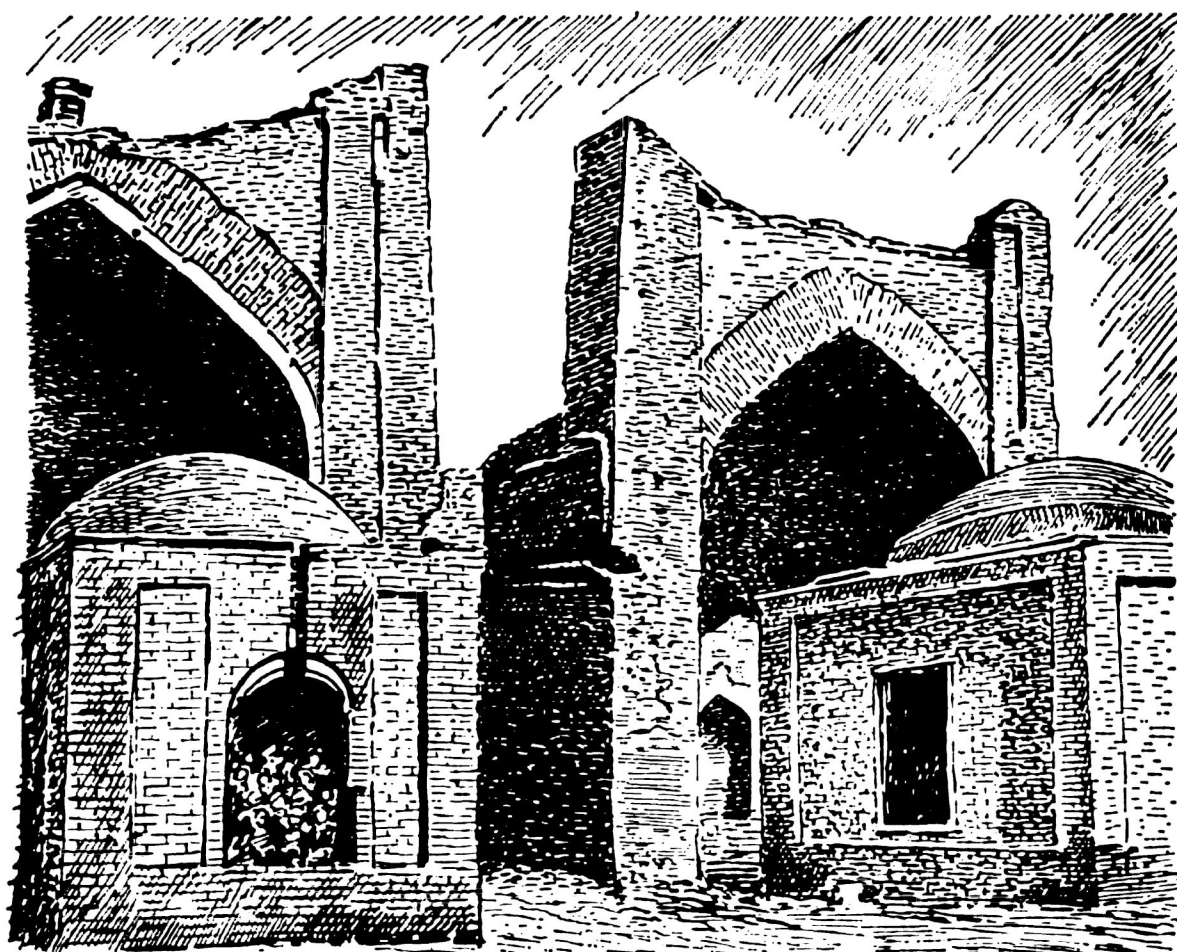


Fig. 60. Deserted ruins, typical habitats of *Ornithodoros* ticks

penetrate into the gastrointestinal tract of the tick from whence they spread to all its organs. Infestation of man: some species of ticks, as, for instance, the vector of Central Asia relapsing fever, transmit the spirochetes directly with their bite; in other species a fluid containing spirochetes is excreted from the coxal glands on its legs while the insect feeds. This fluid contaminates the wound caused by the bite, and thus the infection is transmitted.

Not only adult *Ornithodoros* ticks are capable of transmitting the infection; the larvae and nymphs of these ticks receive the infection by transovarial transmission (this transmission continues for two or three generations), and as they also feed on the blood they are capable of passing on the infection.

### DIFFERENT TYPES OF TICK-BORNE RELAPSING FEVER AND THEIR GEOGRAPHICAL DISTRIBUTION

Relapsing fever is common to 32 countries.

According to the data in *Global Epidemiology* (Simmons, Whayne, et al., 1944-54) it is observed in the following countries: Iraq (up to 100 cases annually), Jordan (140-250 cases), Israel, Lebanon, Syria, Afghanistan, Iran (chiefly its northern regions), Yemen, Sudan, Ethiopia (endemic sites in its eastern part); Somaliland (up to 800 cases); East Africa: Kenya (750 cases), Uganda (1370), Tanganyika (extremely widespread), Nyasaland (700), North and South Rhodesia (over 1,000), Mozambique, Madagascar, the South-African Republic; Equatorial Africa: the Republic of Congo (extremely widespread), Cameroon (extremely widespread); West Africa (sporadic cases); North Africa: Algeria, Tunisia, Lybia (isolated sites); Europe: Spain (southern part). In all these countries, with single exceptions, louse-bite typhus (Fig. 61) is also encountered.

#### Central Asia tick-borne relapsing fever

The disease is caused by *Spirochaeta (Borrelia) sogdiana (uzbekistanica, latishevi)* (Magnitsky, 1922; Pickoul, 1928).

The vector is the tick *Ornithodoros papillipes* — *Alectorobius tholozani* (in accordance with the latest classification worked out by M. V. Pospelova-Strom), *Ornithodoros tartakowskyi*.

Sites: Uzbekistan, Tajikistan, Turkmenistan, Kirghizia, South Kazakhstan.

The disease is common not only to the plainlands, but to mountainous regions as well (Western Pamir, Chimghan, Breach-mullah, etc.).

Tick-borne relapsing fever is an endemic disease. Its isolated foci are predominantly restricted to villages and other rural communities with adobe structures, but it occasionally occurs in cities where there still remain some old adobe buildings. The disease, spread chiefly by the domestic tick *Ornithodoros papillipes*, is common to inhabited communities, but its incidence has also been registered in uninhabited areas, where the infection was transmitted by *Ornithodoros tartakowskyi* (Isayev, 1956), ticks that live in animal burrows.

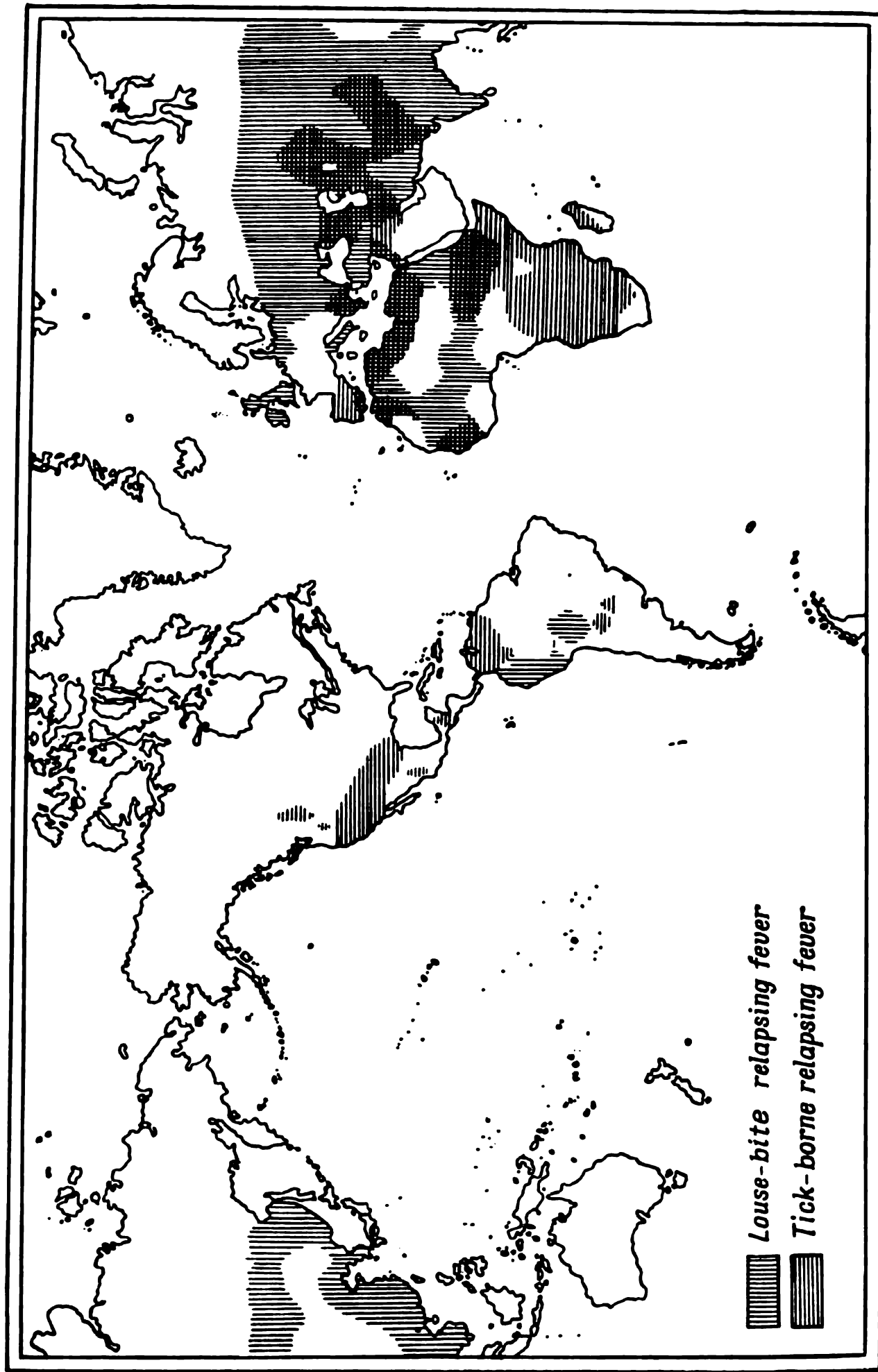


Fig. 61. Geographical distribution of relapsing fevers

The onset of the disease occurs throughout the year, but the incidence is higher in the spring and summer months. A noteworthy point is the existence of various geographic strains of spirochetes that manifest biological differences in adaptation to different species of ticks and in the susceptibility of laboratory animals to them.

### **Turkmen tick-borne relapsing fever**

This form has only recently been set apart as being independent, although neither the biology of its pathogen *Spirochaeta latishevi* (Sofiyev, 1941), nor its clinical findings differ in any manner from Central Asia relapsing fever.

The vector is *Ornithodoros papillipes*.

The reservoir of the infection is principally the gerbil *Rhombomys opimus*. Incidence is endemic in various regions of Turkmenia.

### **Caucasian tick-borne relapsing fever**

Pathogen: *Spirochaeta Caucasica* (Martzinovsky, 1921; Kandelaki, 1928).

The infection is transmitted by numerous rodents.

The clinical findings do not differ from those of Central Asia relapsing fever.

The vector is *Ornithodoros verrucosus* (*Alectorobius asperus*). This tick lives in natural shelters — burrows, caves, etc.

The reservoir of the infection in natural conditions are wood voles, the Caucasian gerbil, common housemice, the jerboa.

The disease appears sporadically among people working in uninhabited areas or visiting such places.

The area of distribution includes the Transcaucasus and Northern Caucasus.

A. I. Isakyan places Armenian tick-borne relapsing fever into a discrete category, holding that *Spirochaeta armenica* (Isakyan, 1936) is an independent species.

### **Persian tick-borne relapsing fever**

Pathogen: *Spirochaeta persica* (Junkovsky, 1912).

Vector: *Ornithodoros papillipes*.

The reservoir of the infection is the same as in Central Asia.

The clinical features of the disease are analogous to the features of Central Asia tick-borne relapsing fever.

Area of distribution: Iran.



### **Western Asia tick-borne relapsing fever**

Pathogen: *Spirochaeta babylonensis*.

Vector: *Ornithodoros papillipes*.

Area of distribution: Syria, Lebanon, Saudi Arabia, Israel, Turkey (Asia Minor).

### **Eastern Asia tick-borne relapsing fever**

Pathogen: *Spirochaeta chinensis*.

Vectors: *Ornithodoros papillipes*, *Ornithodoros verrucosus*.

Area of distribution: south, south-western and south-eastern China, the Indo-China peninsula.

### **Indian tick-borne relapsing fever**

Pathogen: *Spirochaeta carteri* (Carter, 1877; Manson, 1907).

Vector: the oriental bedbugs *Cimex rotundatus* (?) and *Brachydesmus pictus* (?), the ticks *Ornithodoros tholozani* var. *crossi* (Kalza a. Rao, 1951).

Reservoir of infection: mice, rats, wild murine rodents.

Area of distribution: India (only the north-western part of the country).

### **Ukrainian tick-borne relapsing fever**

Pathogen: *Spirochaeta borysthena* (Gromashevsky, Goryacheva, Khoruzhenko, 1956).

Vector: *Ornithodoros verrucosus* (a variant form).

Natural foci: among rodents. Experimentally the spirochete causes the disease in guinea pigs.

The clinical findings are analogous to those of Central Asia and Caucasian relapsing fevers.

The disease was discovered in the Ukraine.

### **Spanish tick-borne relapsing fever**

Pathogen: *Spirochaeta hispanica* (de Buen, 1926), and *Spirochaeta marocana* (Nicolle and Anderson, 1928) (a variant form).

Vector: *Ornithodoros maroccanus*, *Ornithodoros moubata*.

Reservoir of infection: rats, gerbils, shrews, and pigs—animals to whom the ticks often attach themselves.

The disease is encountered in Spain, Morocco, and Tunisia.

The clinical features are the same as in other forms of tick-borne relapsing fever, but the number of attacks is less (4-5). Wood (1954), working on the Island of Crete, described an analogous clinical form with a short incubation period and the same pathogen, presumably transmitted by *Ornithodoros tholozani* (?).

### **North African tick-borne relapsing fever**

Pathogen: *Spirochaeta berbera (aegyptica)*.

Vector: *Ornithodoros savignyi*, *Ornithodoros maroccanus*, *Ornithodoros moubata*.

The clinical features are analogous to those of Central Asia tick-borne relapsing fever.

Area of distribution: U.A.R. (Egypt), Libya, Sudan, Ethiopia, Tunis, Marocco.

### **African tick fever**

Pathogen: *Spirochaeta duttoni* (Novyi and Knapp, 1906).

Vector: a tick of the genus *Ornithodoros*, variety *Ornithodoros moubata*.

Reservoir of infection: rats, shrews, and other rodents.

Clinical features and pathogenesis are analogous to those of other tick-borne relapsing fevers.

Area of distribution: Central, Eastern, Western and Southern Africa.

### **North American and Mexican tick-borne relapsing fever**

Pathogens: *Spirochaeta turicata* (Shellake, 1907); *Spirochaeta parkeri* (Davis, 1942); *Spirochaeta hermsi* (Davis, 1942).

Vectors: *Ornithodoros turicata*, *Ornithodoros parkeri*.

Reservoir of infection in natural foci — murine rodents (the Mexican field-mouse *Microtus mexicanicus*) and other animals.

The clinical features are analogous to other forms of tick fevers.

Area of distribution: western states of U.S.A. — California, Colorado, and also Mexico.

### **South American tick-borne relapsing fever**

Pathogen: *Spirochaeta neotropicalis (venezuelensis)* (Brumpt, 1921).

Vectors: *Ornithodoros venezuelensis* (in Venezuela), *Ornithodoros talajae* (in Panama, Colombia, Bolivia, Argentina, Brazil, etc.).

### **LABORATORY DIAGNOSIS**

It is usually difficult to demonstrate the spirochetes in thin smears of peripheral blood as such examinations call for scrupulous investigations taking up several hours. The thick film method is better suited for diagnosis. This method yields positive results in 2-3 to 20-30 minutes of examination.

In 1921, Y.I. Martzinovsky stated that the spirochetes should be demonstrable in the peripheral blood during the apyrexial period of relapsing fever; this opinion has now been confirmed (true, the demonstration calls for an assiduous search).

In bone marrow specimens the spirochetes are discovered predominantly during paroxysms (authors' observations).

During apyrexial interludes (the day following an attack, and the third day) no spirochetes are demonstrable in thick films of bone marrow specimens.

A low concentration of spirochetes is presented in various organs and excreta: in the liver, spleen, bone marrow, cerebrospinal fluid, urine, etc., but the predominant location is the brain.

Some species of spirochetes are retained in the organs, particularly in the brain, for several months after the last paroxysm of the disease.

Moretti proved the presence of spirochetes in the brain of experimental animals for a period of 103-107 days after they had left the peripheral blood (*Spirochaeta duttoni* disappeared from rat blood on the 261st day, while an emulsion of the brain of this rat was effective in transmitting the infection to another rat).

The xenoinjection method may be recommended for diagnostic purposes (for *Spirochaeta sogdiana* guinea pigs are used).

Spirochete concentration is also employed for diagnosing tick-borne relapsing fevers.

#### CLINICAL ASPECTS

The incubation period is 6 to 14 days. The onset of the disease is the same as in louse-bite relapsing fever; it is commonly sudden, or is preceded by a short prodromal period with symptoms of generalised weakness, indisposition, headache, pains in the extremities, and light chills. Several patients observed by the authors noted these symptoms, as well as pain in the small of the back 3-4 days prior to an attack. In some cases the temperature does not immediately jump to high levels, but remains at 38-38.5 °C. It may subsequently go up to 39.5-40°C.

The excitability associated with the fever resembles the behaviour of patients with louse-bite relapsing fever, but is less pronounced.

Severe headache is a frequent and characteristic symptom of tick-borne relapsing fever; however, loss of consciousness was seen in only one of the 78 cases observed by the authors, and that for a very short time (during the night).

The duration of the first attack varies from 24 hours to 3-4 days, after which the temperature may fall below normal or oscillate within a range of 36.8-37.5 °C throughout the apyrexial interval.

Defervescence is commonly attended by profuse sweating, although some patients may perspire very little; in any case, this symptom is likewise not as distinct as in louse-bite relapsing fever.

After the fever has subsided the general condition of the patient improves quite rapidly (usually by the very next day), the opposite of what is seen in louse-bite relapsing fever. Patients may even feel well enough to resume work.

The relapsing fevers usually manifest a sudden pyrexial onset (up to 39°), the temperature peak holding for one or two days, followed by a one-

-day remission that is succeeded by another peak, a longer apyrexial period (3-6 days) and once more febrile periods with remissions either in the morning or on alternate days. Subsequently the attacks appear over intervals of 5-7 days and last no longer than 12 to 18 hours. In other cases the attacks display a monothermal temperature lasting 2-5 days; however, tick-borne relapsing fevers are almost invariably characterised by wide oscillations of temperature and apyrexial remissions. Defervescence is usually accompanied by profuse sweating.

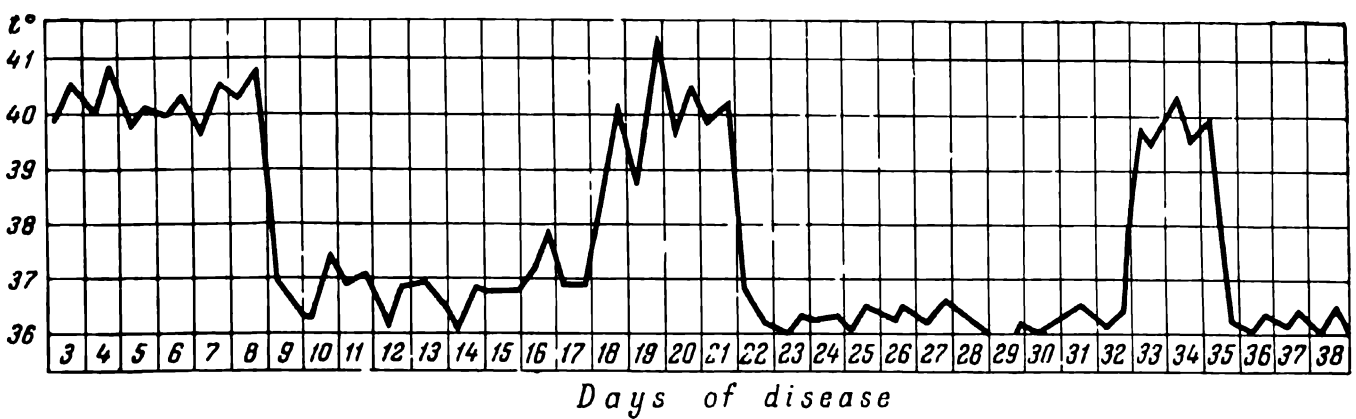


Fig. 62. Temperature curve in European relapsing fever

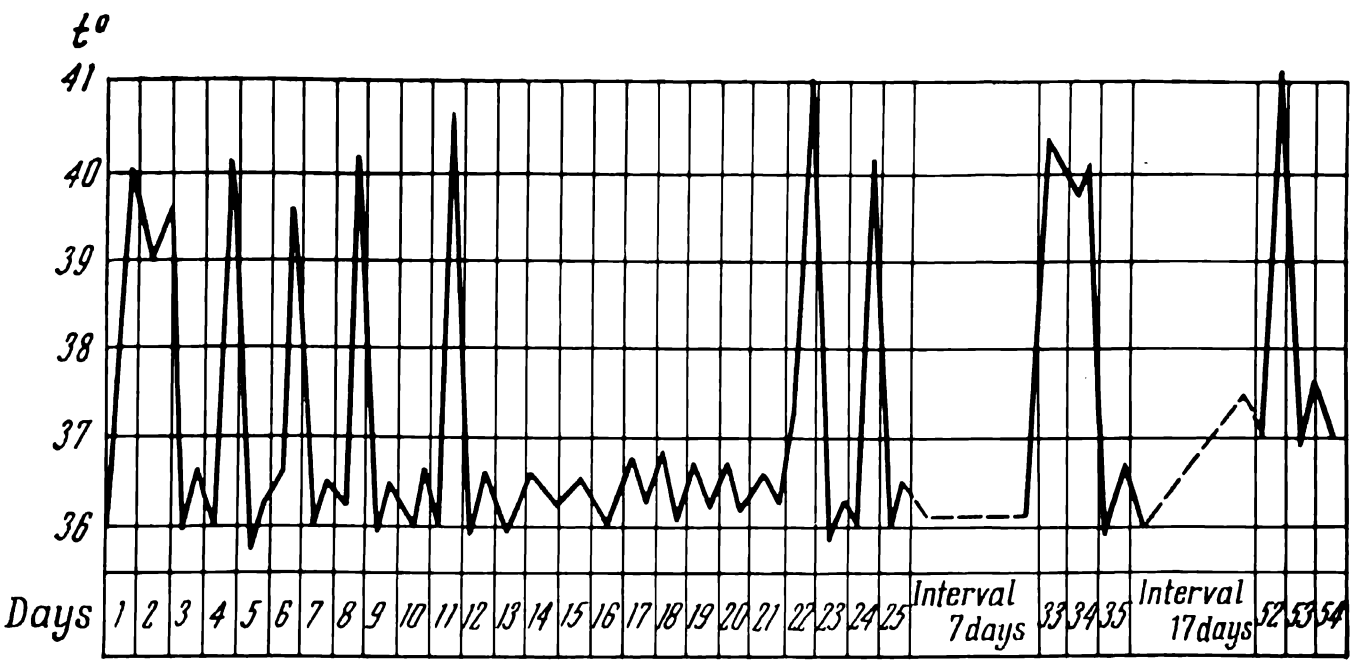


Fig. 63. Temperature curve in tick-borne relapsing fever

Other points of interest found by the present authors were extremely protracted initial attacks (6-7 days) with short remissions, and cases where the fever was of such short duration (6 hours) that it did not affect the temperature curve (when it occurred at night).

There are also cases in which the fever is intermittent at the onset of the disease, like in tertian malaria, or when this type of fever occurs at the middle phase of the disease.

Profuse sweating usually accompanies the decrease in temperature. The average number of attacks is 8-10, but in one case it was observed to total 20. The duration of the disease is from 20 to 50 days and more (2½-3 months) (Figs 62 and 63).

*Cardiovascular* involvement in tick-borne relapsing fever is relatively rare.

The *gastrointestinal tract* suffers little from this disease. The tongue is slightly coated; this white film disappears in the apyrexial period. Appetite is low during attacks, but normal in the intervals between them.

As a rule, the *spleen* enlarges as the disease progresses; its edge is usually palpable 1-2 cm beneath the lower edge of the ribs; if the organ is not palpable its enlargement upwards can be detected by percussion (up to the eighth rib along the midaxillary line). The spleen is slightly hardened, but not painful, contrary to what is observed in louse-bite relapsing fever. The authors have noted no complications in the spleen (infarction, abscess), although reports of such cases have been published.

The *liver* also becomes enlarged in all directions, but not very much, 1 cm at the most. It is slightly firmer than usually, palpation ordinarily evokes no pain.

The *blood picture* also shows some quantitative differentiation from louse-bite relapsing fever, while the qualitative changes are approximately the same. In the red blood a slight hypochromic anemia is noted; it develops toward the end of the disease, after 6-10 paroxysms. The changes in the white blood are more spectacular. Moderate leukocytosis is commonly observed during attacks (8,000-10,000), although higher counts have also been noted (up to 12,000). The differential white blood count during an attack shows a slight predominance of neutrophils, therefore the absolute values of these cells are undoubtedly increased. An increase of band-like neutrophil leukocytes is noted. Occasionally a moderate monocytosis (up to 10 per cent) is observed during attacks.

During the apyrexial interludes and after final convalescence the number of leukocytes returns to normal, while the differential count shows an increase of lymphocytes to 30-45 per cent, of monocytes to 10-12 per cent, and of eosinophils to 5 per cent.

An infectious type of albuminuria of a transient nature is observed in the urogenital tract.

*Complications.* Certain forms of tick-borne relapsing fever (Central Africa, East Africa, Mesopotamia, and other types) are characterised by a severe clinical course (as in louse-bite relapsing fever), and by a number of commonly-known complications (jaundice, pneumonia, nephritis, sepsis, eye trouble, otitis, etc.).

N. V. Troitzky (1926) described a case of severe parenchymatous hepatitis with jaundice that terminated lethally (in Baisun). This researcher exposed himself to experimental infection (by feeding *Ornithodoros papillipes* ticks on his body) and suffered a complication — opacification of the vitreous accompanied by temporary loss of sight. An analogous complication was suffered by N. I. Latyshev (1926) who also exposed himself to tick bites and contracted relapsing fever.

It is noteworthy that both these researchers continued their microscopy studies even during paroxysms of fever.

The clinical course of the disease is generally mild; it is only during some outbreaks that the disease acquires a more severe form and terminates

lethally (according to N.V. Troitzky in 2-4 per cent of cases). During the apyrexial intervals, particularly in the 2nd or 3rd week of the disease, when the remissions increase to 10-15 days, the patients feel quite well.

### DIFFERENTIAL DIAGNOSIS

In the differential diagnosis of tick-borne relapsing fever the disease has mainly to be distinguished from louse-bite relapsing fever, malaria, dengue and pappataci fever. Tick-borne relapsing fever differs from the first of these diseases by its temperature curve, by an insignificant and much slower enlargement of the spleen, and by the low concentration of spirochetes in smears of peripheral blood. Tick-borne fever is easily confused with malaria, all the more so since its temperature curve at times is very similar to that of malaria.

These two diseases are differentiated by the much greater enlargement of the spleen in malaria (although this is not a constant symptom) and its tenderness, and, principally, by repeated thorough blood tests.

It is easy to confuse pappataci fever with tick-borne relapsing fever during the first days following its onset, or during a relapse. Here, too, blood tests and the different temperature curves will help in the establishment of the true diagnosis.

### TREATMENT

The spirochetes responsible for tick-borne relapsing fever are morphologically identical with the spirochetes that cause louse-bite relapsing fever, but their sensitivity to salvarsan preparations is very low.

Tick-borne relapsing fever is an illustrative example of the resistance of spirochetes to salvarsan.

The authors had under their observation 78 patients with tick-borne relapsing fever whom they treated with novarsenol (a Soviet brand of neoarsphenamine) and osarsol (acetarsone, Soviet brand) in variant doses. It was found that the administration of novarsenol (0.45-0.5 g) did not, as a rule, curtail the paroxysms or prevent relapses; however, prolongation of the apyrexial periods and moderation of the clinical features were observed (decrease of temperature to 37.8-38 °C).

I. Y. Monakrovich gave 0.3 g doses of novarsenol for as many as 5-6 times over intervals of 5-6 days; he noted recovery of a number of patients, although in other cases there were relapses even after 5 injections of novarsenol. According to the latest reports of the malaria stations in the Uzbek Republic half of the cases of tick-borne relapsing fever are curtailed by novarsenol administered by the following plan: an 0.3 g initial injection and two days later a dose of 0.45-0.5 g.

One or two six-day osarsol (acetarsone, acetarsol) courses proved ineffective; four or five courses prolonged the apyrexial periods and decreased the temperature, but in several instances proved completely ineffective. However, taking into consideration the low efficiency of osarsol, such

persistent treatment with this agent should not be resorted to, as in a number of cases it may produce undesirable side effects (the authors have observed several cases of nephritis, two cases of encephalitis in a mild form, several cases of osarsol skin rashes accompanied by rises in temperature and severe headache). The authors have also observed a relapse of tick-borne fever after a very protracted erroneous course of treatment with osarsol administered by an inexperienced doctor (0.25 g 3 times a day for 16 days).

Z. S. Nikolayevskaya (1947, 1955) demonstrated, in extensive experiments on mice infected with Asiatic spirochetosis (Iranian, Daghestan, and Jalangarian strains), that penicillin injected on 3 consecutive days in doses from 4,000 to 15,000 units freed these animals of the pathogenic spirochetes.

Some authors employ penicillin therapy in combination with novarsenol. Penicillin doses of 200,000 u are injected 3-4 times a day for 10 to 14 consecutive days. As a result the paroxysms of the disease are noticeably reduced in approximately half of the patients. However, all the above methods of treatment are only of relative merit. Of late a more effective method has been evolved in the treatment of tick-borne relapsing fever — treatment with biomycin (aureomycin). In experiments on guinea pigs P. K. Ibragimov (1958) obtained no effect with penicillin; biomycin likewise did not check the disease, it only lowered the spirochetemia temporarily. This preparation was successfully used by A.V. Yeremyan (1954) in cases of Asiatic tick-borne relapsing fever. Gimeno de Sande (1953) showed the undubitable efficacy of aureomycin therapy in tick-borne fever on 68 patients. He recommends the following method of aureomycin therapy which may be recommended for clinical practice: six initial doses of 0.5 g are given during one day (a total dose of 3 g); further the dosage is lowered to 2 g per day. The preparation is administered until a stable effect is obtained. The temperature goes down in 12 to 24 hours. Terramycin is less effective.

### PROPHYLAXIS

The first and foremost measures of prophylaxis are the extermination of the *Ornithodoros* ticks. It has been proved possible to considerably lower the incidence of relapsing fever and even extinguish its sites by extermination of the ticks with DDT and hexachlorane preparations (L. M. Isayev, 1956). A dose of 1 g of the active substance applied to 1 sq m of surface proved sufficient for destroying the younger generation of larvae and nymphs and the overwhelming majority of older nymphs and males and females within 5 to 10 minutes after they had contacted the insecticide-treated surfaces.

The present authors prefer hexachlorane preparations, as these substances possess, apart from contact action, also a fumigating effect (ticks have been observed to perish even at a distance of 10-15 cm from insecticide-treated surfaces). The preparations are applied chiefly to floors,

cracks in houses, and to walls (only up to a man's height, as the ticks do not go up high).

The most effective results in gaining control of ticks are obtained in the months of March and April (the period of activity of the ticks), and in July and August (for exterminating the larvae hatched out of the eggs).

The next important step in combating tick-borne fever is extermination of rodents, principally house-rodents: rats, mice, gerbils, etc., and keeping check of morbidity among domestic animals.

Prophylactic measures directed at preventing the spread of tick-borne relapsing fever also include the careful whitewashing and plastering of living quarters, animal sheds, barns and similar structures, and the sealing of cracks with lime-paste.

For individual prophylaxis it is recommended to avoid sleeping in adobe houses, huts, outhouses, caravansaries (roadside inns); if this is unavoidable tin cans holding water or kerosene should be placed under the bed-legs (Y. N. Pavlovsky, 1944).

The incidence of tick-borne relapsing fever in Central Asia and the Caucasus went down very considerably in the 1950's (only sporadic cases are now registered) owing to vigorous measures taken against it.



# LEPTOSPIRAL DISEASES OF MAN

---

Synonyms: leptospirosis (Lat., Engl.), Leptospirose (Germ.), léptospirose (Fr.).

Icteric and non-icteric leptospiroses are a group of infectious diseases of the septic type. A characteristic feature of the infection is that it exists endemically in natural foci among wild rodents, although epizootic outbreaks may also occur among domestic animals — house-rodents, cattle, dogs. The basic source of infection is water and food contaminated with the excreta of infected animals.

Although leptospirosis is encountered widely, it is predominantly a disease of warm lands (particularly some of its forms).

## HISTORICAL DATA

Leptospiral infections were recognised as a discrete disease about 75 years ago, although, judging by existing descriptions, they had been observed long before that.

The first comprehensive description of spirochetel jaundice (icteric leptospirosis) and its classification as an independent type was made in 1886 by Weil. The Russian researcher S. P. Botkin (1886) instructed his pupil N. P. Vasilyev to collect and summarise clinical observations of analogous cases registered in his clinic since 1883. The *Yezhenedel'naya Klinicheskaya Gazeta* (*Weekly Clinical Review*) for 1888 carried a number of articles in which Vasilyev reported on 17 cases of infectious jaundice of the Weil disease type, giving a circumstantial clinico-anatomic characteristic of the disease and confidently affirming it to be an independent form.

In February 1915, the Japanese researchers Inada, Ido, Hoki, Kaneko and Ito published a work in which they described as the causative agent of Weil's disease a new species of spirochete that they called *Spirochaeta icterohaemorrhagiae*. In September-October of that same year the German microbiologists Hübner, Reiter, Ulenhuth and Fromme reported discovery

of spirochetes in the liver of a guinea pig that had died with symptoms of jaundice after having been inoculated with the blood of patients. They called this spirochete *Spirochaeta nodosa*, *Spirochaeta icterogenes*. In 1917, the Japanese microbiologists Noguchi isolated the spirochete from a patient and proposed the name *Leptospira* for this newly discovered genus.

Subsequently descriptions of leptospirosis with or without jaundice appeared in the Far East, south-eastern Asia, and other countries of the world.

In 1927, V. A. Bashenin was the first in the U.S.S.R. to single out marsh fever as a discrete nosologic form, and in 1928, S. I. Tarasov and G. V. Epstein isolated a culture of the causative agent morphologically identical with the icterohemorrhagic spirochete, but differing from the latter in some of its serological and biological features. Tarasov called this pathogen *Leptospira grippotyphosa*.

Subsequently scientists the world over established, and still continue to establish, other serological types of *Leptospira* in various countries. Their number is at present very great. In the U.S.S.R. signal success must be accredited to V. I. Terskikh, K. N. Tokarevich, A. A. Varfolomeyeva, V. S. Kiktenko and other researchers for their efforts aimed at expanding knowledge on leptospirosis, for the discovery of new forms of the disease and new serological types of leptospire. And so, we repeat, the pathogen of leptospirosis is the genus *Leptospira*. Comprehensive investigations have been made to date of its morphological structure (even with the electron microscope). The typical leptospire body consists of a long spiral filament with hooked ends. The leptospire measures 10-15 microns in length, young forms are shorter, while in old cultures some individuals may be as long as 50 to 150 microns. The breadth of the leptospire is 0.2 to 0.25 microns. The coils of the spiral are very small (0.5 microns amplitude) and arranged in such close apposition that they are discernible only in dark-field illumination, or with special stains (silver method).

The staining techniques employed for leptospire are generally analogous to those employed in the examination of the etiological agent of syphilis (*Spirochaeta pallida*).

The life history of the *Leptospira* has still to be gone into more deeply. The organisms multiply by transverse fissure. Although it has been contended that there exists a filtrable stage of leptospire the majority of authors consider that the visible forms are the only possible form of existence of these parasites. In the outer environment the saprophytic and pathogenic leptospire can presumably exist only in water or moist soil. Acid media destroy them, but in alkaline water they subsist for a long time: when cultivated in sterilised tapwater leptospire can live for 3 to 8 months without passage (V. S. Kiktenko, 1954), while they soon perish in non-sterile water. These organisms are unstable against heat, but low temperatures are well tolerated. Leptospire are cultivated in special media (Zuelzer, Fletcher).

In accordance with clinical findings leptospiral diseases may conditionally be divided into icteric (the Weil-Vasilyev disease) and non-icteric forms (marsh fever of various localities).

Eleven serological and biological basic types of leptospires and two subtypes have been identified in the U.S.S.R. (V. S. Kiktenko, 1954), one of which is a saprophyte (*Leptospira biflexa*). To date 8 leptospiral diseases of man and animals have been described in the U.S.S.R.: the Weil-Vasilyev disease, marsh fever, Rostov infectious jaundice, FE-A and FE-B fevers, icterohemoglobinuria of horned cattle, seven-day fever, and canine leptospirosis. All these diseases are caused by six types and two subtypes of leptospires pathogenic to man and particularly to animals (Kiktenko). Moreover, lately *Leptospira acrinacei auriti*, *L. sorex*, *L. nero*, and *L. bataviae* have been discovered (as yet only in animals) in the U.S.S.R.

#### **SPIROCHETAL JAUNDICE (ICTEROHEMORRHAGIC LEPTOSPIROSIS, WEIL-VASILYEV DISEASE)**

Synonyms: leptospirosis icterohaemorrhagica, morbus Weil-Vasilyev (Lat.); icterohemorrhagic spirochetosis, Weil's disease, leptospiral jaundice (Engl.); Weilsche Krankheit (Germ.); leptospirose ictero-hemorrhagique, la maladie de Weil (Fr.); enfermedad de Weil (Sp.).

#### **Etiology**

The causative agent is *Spirochaeta icterohaemorrhagiae* (Inado, Ido, 1914); *Leptospira icterohaemorrhagiae* (Noguchi, 1917); *Spirochaeta icterogenes* (Uhlenhuth, Fromme, 1915); *Spirochaeta nodosa* (Heubener, Reiter, 1915) (Fig. 64).

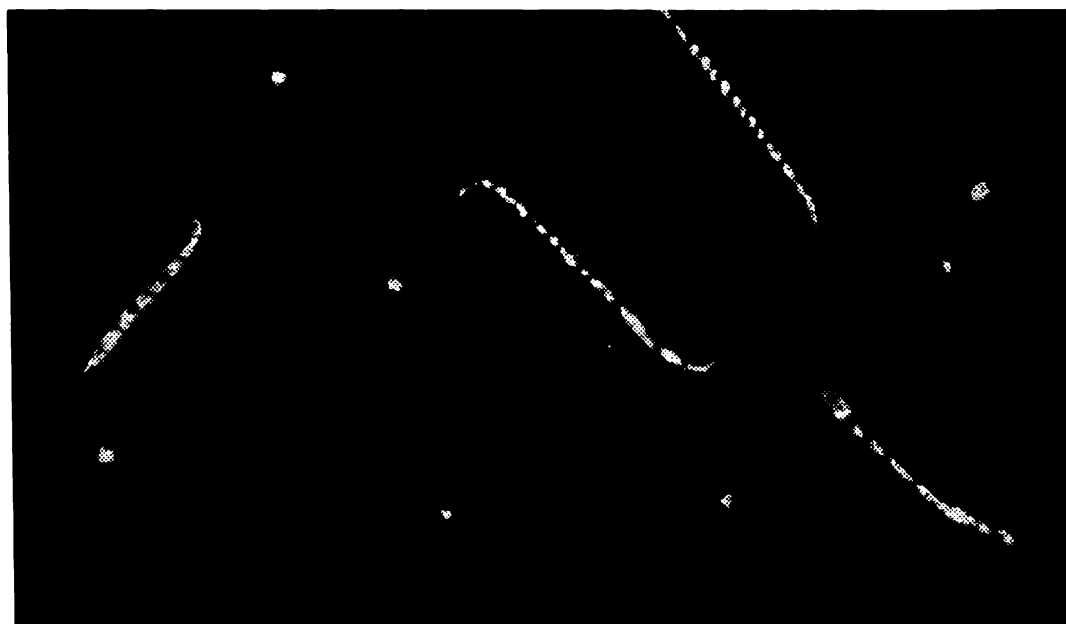


Fig. 64. Leptospires in dark-field illumination, magnification 1320 × (original)

*L. icterohaemorrhagiae* is pathogenic to man, dogs, foxes, young guinea pigs, a number of rodents (gophers, rats). The infected animals perish with symptoms of jaundice and hemorrhagic diathesis.

Serologically *L. icterohaemorrhagiae* has been singled out as an independent type, but some authors (A. A. Varfolomeyeva and others) hold that there exist two varieties of spirochetes (?).

The disease is caused by the penetration of the leptospire into the body through the alimentary tract, mucous membranes (e. g., of the eyes), skin lesions (wound surface, hangnail, etc.).

The disease is a septicotoxic process during which the leptospire is predominantly located and multiplies in the blood, and subsequently in the liver and kidneys. Beginning with the second week the organisms are found in the urine.

### Distribution and epidemiology

Spirochetel jaundice is found everywhere. It is particularly widespread in countries where poor sanitary conditions are conducive to contamination of water supplies by rodents. There are grounds for assuming that during World Wars I and II outbreaks of spirochetel jaundice (not identified bacteriologically but clearly denoted clinically) occurred in a number of countries.

In the U.S.S.R. there was, on the whole, only a small number of proved cases of this disease.

In Europe quite a large incidence was registered in the Netherlands (756 cases in 1936), in Germany (644 cases from 1939 through 1943), in France (263 cases from 1924 through 1932), in Britain (248 cases from 1924 through 1938), in Italy, Switzerland, Czechoslovakia, and other countries. Small outbreaks were described on the American continent.

V. S. Kiktenko (1954) points out that spirochetel jaundice is particularly widespread in tropical and subtropical countries. Considerable outbreaks of the disease were registered in Japan (6,000 cases in 1917 and 1,636 cases in 1933). Quite a large number of cases were likewise observed in India, Indonesia, Indo-China, etc.

The *source of infection* of man are rats *Rattus norvegicus* and *Rattus rattus*. The percentage of *Leptospira*-carriers in various countries ranges from low (1-2) to high (50-70) figures. In rats the leptospire is concentrated chiefly in the kidneys. They are washed out with the urine, contaminating water and food, and thus infecting human beings (Figs 65, 66, 67). Man also passes leptospire with urine from the second to sixth week of the disease; however, the practical significance of the infectiousness of human urine is negligible. The widespread distribution of great numbers of rats, poor sanitary conditions (negligent care of food), unprotected water sources — these are all factors promoting the dissemination of the disease. The epidemiological premises of an outbreak of spirochetel jaundice in Leningrad during the siege of this city in the last war constitute an interesting point. During the frequent bombings the city's water mains were destroyed; water filled up the cellars, drowning great numbers of rats. People who drank this contaminated water contracted spirochetel jaundice.

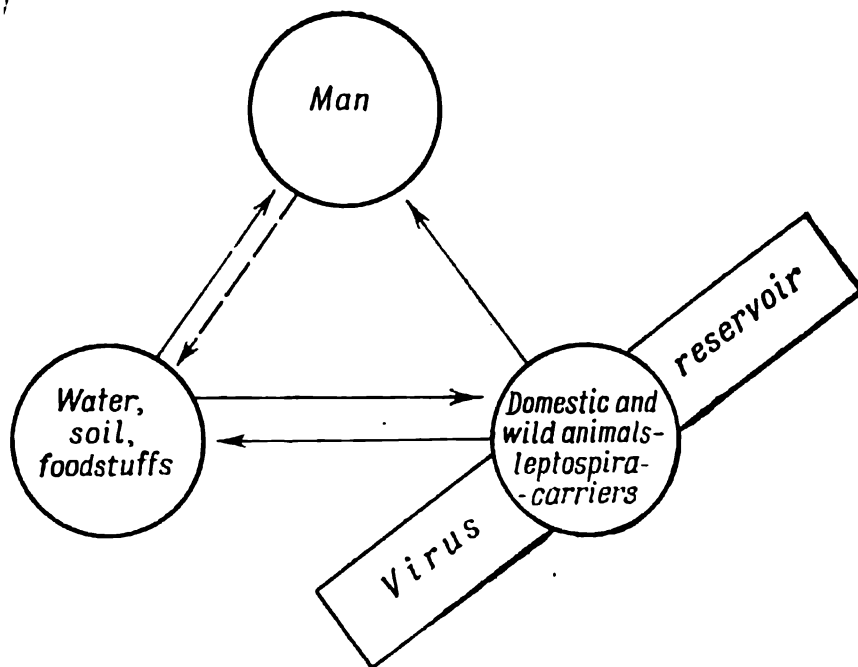


Fig. 65. Circulation of pathogenic leptospires in nature (V. S. Kiktenko)

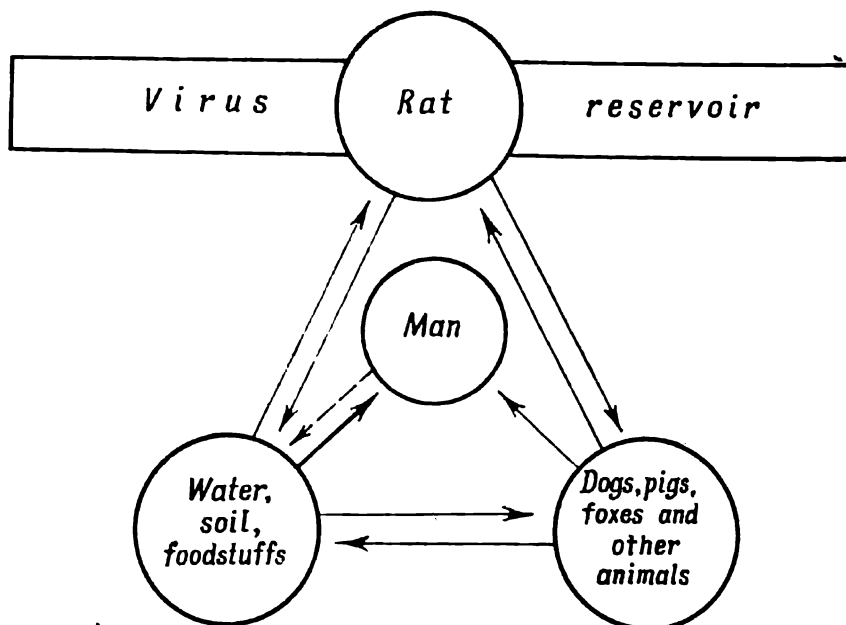


Fig. 66. Circulation of pathogen of Weil-Vasilyev disease in nature (V. S. Kiktenko)

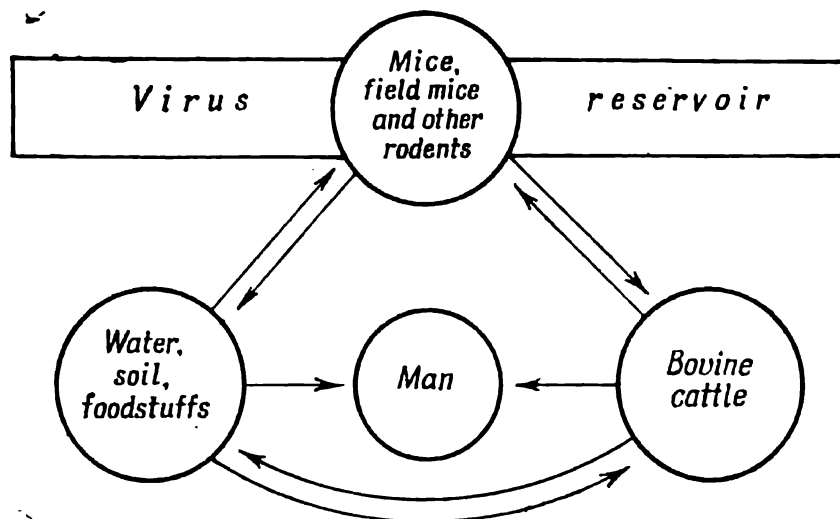


Fig. 67. Circulation of pathogen of non-icteric leptospirosis in nature (V. S. Kiktenko)

The association of the infection with water is beyond doubt. Many reports have been published on cases of spirochetel jaundice contracted by man through contact with contaminated water (while bathing, for instance).

There are various possible routes of human infection; these routes depend on the virulence of the pathogens, susceptibility, and other factors. The incidence is higher during the summer and autumn months, although in a number of tropical and subtropical lands the disease is observed throughout the year. The greater incidence of morbidity during the summer and autumn in countries of continental climate is due to a higher survival of the leptospire in the outer environment during these months, and also to the greater contact man has with water, soil, etc., in these seasons (V. S. Kiktenko). The number of rodent leptospira-carriers also increases at this time.

### Clinical aspects

The clinical features of the disease are quite diversified. During one and the same epidemic both very severe and very mild cases are observed. In certain countries (Japan, for instance) the clinical course is more severe than in others (in northern lands, for instance). Clinical variations depend both on the natural virulence of the infection and on the condition of the affected individual; the symptoms are graver in weakened, emaciated, vitamin-deficient patients; much depends on the condition of the liver. Young people tolerate the disease more easily, while elderly people have greater difficulty in getting over it. The severity of the course of the disease is also associated with the intensity of the jaundice; cases with light jaundice are much milder than cases in which the jaundice is well expressed.

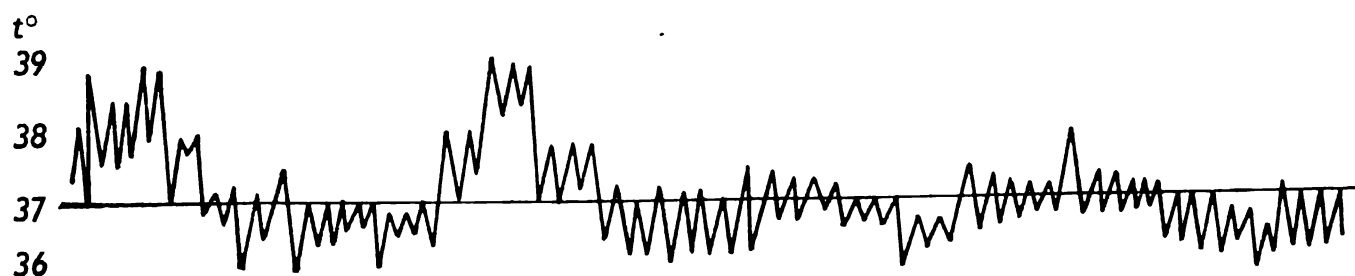


Fig. 68. Temperature curve in Weil-Vasilyev disease (three waves)

This may be illustrated by the description of the course of spirochetel jaundice of moderate severity.

The incubation period is usually 7-10 days, but it may last as long as 2 weeks. The onset of the disease is usually sudden, with no prodromal symptoms, beginning with slight or severe chills. The temperature goes up at once to 39-40 °C (Fig. 68). This hyperthermy is accompanied by nausea, occasionally by vomiting, diarrhea, severe headache and intensive muscular pain. The high temperature usually persists for 5 to 9 days, after which it goes down, in a serrated curve, to normal or subfebrile values. In 70 per cent of cases a second paroxysm occurs after 5-10 days, lasting for 5 to 10 days. In some cases another one or two febrile attacks occur. Occasion-

ally no undulations in the fever are noticed. The disease usually terminates in 3-4 weeks, but in some persistent relapsing cases may go on for 1½ months.

An early appearance of muscular pain is very characteristic of spirochetal jaundice (pains in the gastrocnemius muscles, the muscles of the neck, back, and abdomen). This pain appears spontaneously, but it is intensified by light palpation. Many years ago N. P. Vasilyev wrote that the muscular pains attendant on this form of hepatitis are much more severe than in any other disease observed by him. The severe pain often forces the patient to keep his head in a rigid position, and this seeming rigidity of the neck may be very misleading, providing grounds for diagnosing meningitis. Arthralgia is frequently observed.

*Nervous system symptoms.* Marked nervous symptoms are particularly typical of spirochetal jaundice. From the very onset of the disease persistent headache, insomnia, restlessness and vomiting appear. These symptoms continue throughout the entire pyrexial period, at times becoming very severe. In 10-15 per cent of spirochetal jaundice cases a true meningeal syndrome is observed with corresponding changes in the cerebrospinal fluid (pleocytosis, positive protein reactions).

The *skin* and the *mucosa*. The external aspect of the patient is quite characteristic: from the very first days of hyperpyrexia his face is flushed and excited, the conjunctival vessels are bloodshot. Catarrhal signs are visible in the fauces; the patient complains of pain or irritation while swallowing.

A. L. Myasnikov (1946) noted herpes on the lips, wings of the nose, and even on the cheeks and forehead in 25 per cent of cases, and approximately as many cases of symmetrical polymorphous erythematous measles-like eruptions on the chest, back, abdomen and extensor surfaces of the extremities.

The icterus only appears on the 4th to 8th day of the disease. Its intensity varies, in some cases being moderate (3-4 mg % of bilirubin in the blood), in others very intensive (saffron jaundice, up to 20-30 mg % of bilirubin in the blood). Symptoms of hemorrhagic diathesis appear in severe cases during the icteric period: petechial rash, hemorrhages into the skin and mucous membranes, as well as bleeding from the gums, nose, and intestine.

The *gastrointestinal tract*. Besides dyspeptic disturbances (nausea, aversion to food, vomiting) various intestinal disorders are noted including constipation or diarrhea of the enterocolitic type, occasionally blood in the stool; the stool is not always acholic, it sometimes retains a light yellow colour.

The *liver* is always enlarged; this is defined by palpation and percussion.

The *spleen*. Enlargement of this organ is established in half of the cases by palpation and still oftener by percussion.

The *kidneys*. Renal involvement is typical of spirochetal jaundice: in some cases nephritis develops either directly following the onset of the disease, or somewhat later. Urinalysis shows albumin, erythrocytes,

granular and hyaline casts. The concentration of residual nitrogen in the blood occasionally increases. No edema is usually observed.

During the period when the jaundice fades a transient polyuria appears; however, albumin traces and microhematuria persist until stable recovery is attained.

Throughout the entire icteric period urinalysis demonstrates bilirubin, bile acids and, in so far as the stool is often not acholic, urobilin (a manifestation of deficient liver function).

The *blood*. Characteristic changes occur in the blood. The most noticeable feature is the development of hypochromic anemia (6.6-8.5 g %Hb and 2,500,000-3,500,000 erythrocytes) that intensifies from the onset of the disease and attains its peak at the end of the icteric period. During the convalescent period a moderate or marked reticulocytosis is observed. The hemogram shows, as a rule, neutrophilic leukocytosis (12,000-20,000). The leukocytosis is particularly high in severe cases accompanied by high temperature. By the time the fever subsides and the jaundice fades the leukocyte count gradually returns to normal. The differential white count is characterised by an increase of younger neutrophil forms, including metamyelocytes and even myelocytes. The eosinophil count drops to 1-2 per cent, occasionally aneosinophilia is noted.

Symptoms of hemorrhagic diathesis are associated with a decrease of thrombocyte counts below critical values (10,000-25,000), as well as with coagulation disturbances conditioned by prothrombin deficiency. In a few cases increased friability of the blood vessels has been observed (positive reactions to the suction [or pinch] and tourniquet tests).

Contrary to what is observed in the Botkin disease (epidemic jaundice or infectious hepatitis) the ESR is accelerated from the onset of the disease. The highest figures are concomitant with the febrile periods.

The *cardiovascular system*. At the height of the disease the pulse rate is accelerated, while arterial pressure is frequently decreased. In a number of cases sudden collapse has been observed.

The *respiratory organs*. Bronchitis is frequent (in 40 per cent of cases), in severe cases a cough that brings up a blood-stained sputum is present.

*Complications*. The complications most frequent are massive pneumonia, cardiac muscle involvement, pericarditis, exudative pleurisy, otitis and parotitis, lymphadenitis. Ophthalmic complications are quite typical in the form of conjunctival or retinal hemorrhage, iritis, iridocyclitis, occasionally retrobulbar neuritis.

Acute hepatic dystrophy is uncommon.

## Diagnosis

The principal diseases with which spirochetal jaundice is compared for differential diagnosis are epidemic jaundice, yellow fever and various icteric conditions connected with liver disorders (icteric cholangitis of various origin, obstructive jaundice).



Botkin's disease (epidemic jaundice) is in the majority of cases not accompanied by high temperatures or septic symptoms. The blood shows a tendency to leukopenia with relative lymphocytosis. Spirochetal jaundice is characterised by septic manifestations, neutrophil leukocytosis and accelerated ESR.

Spirochetal jaundice is easily confused with yellow fever (severe clinical course, leukocytosis); however, in spirochetal jaundice the black vomitus so characteristic of yellow fever is never present, and the feverish period is more protracted; spirochetal jaundice is occasionally complicated by meningitis and pericarditis, while yellow fever never is. The decisive factor, however, in any difficult case is laboratory diagnosis.

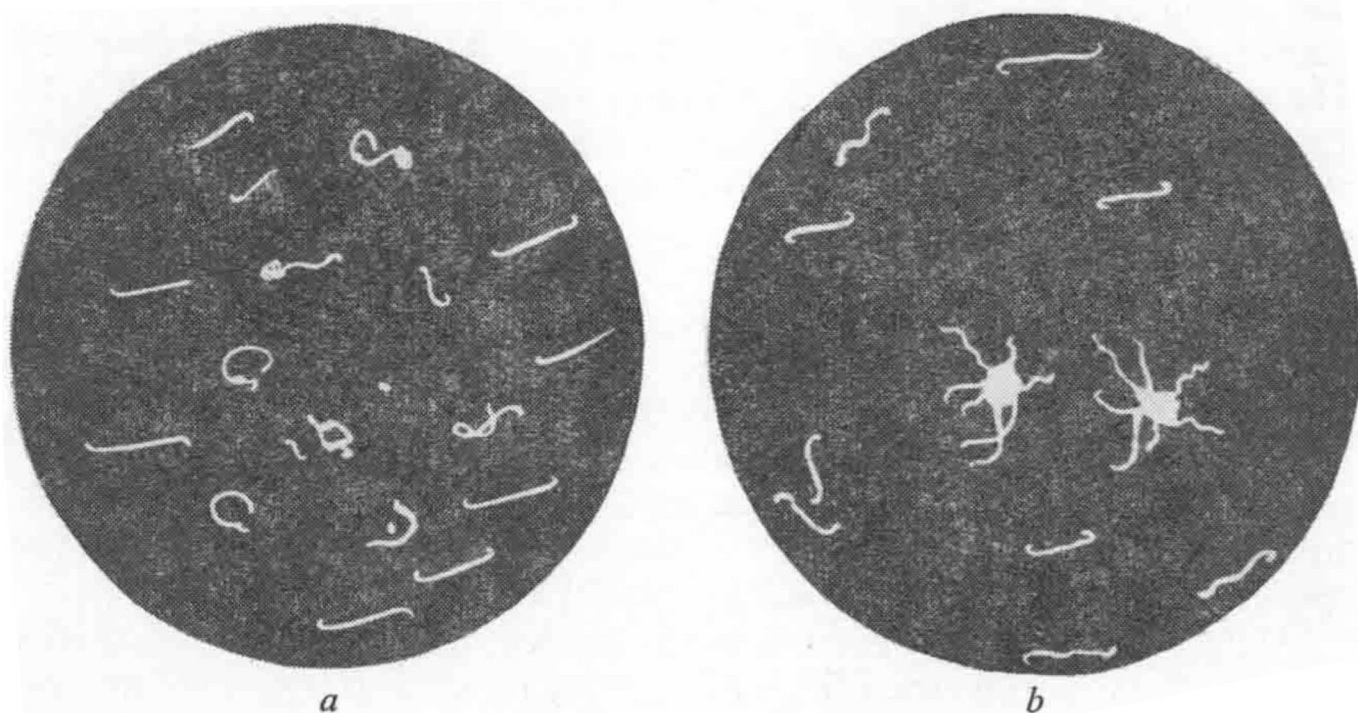


Fig. 69. Agglutination of leptospires. *a*—individual; *b*—with formation of “spiders”

Various secondary jaundices are easily distinguished from spirochetal jaundice. Such secondary conditions are icteric typhoid developing on the basis of louse-bite recurrent typhus, or cholangitis that complicates septic and infectious diseases or acute cholecystitis.

*Laboratory diagnosis* for spirochetal jaundice is quite well-developed currently; however, it still calls for the employment of special techniques.

The quickest method for discovering the leptospires is dark-field microscopy of fresh specimens of the patient's blood; the disadvantage of this method is the requirement that the investigation be made within the first five days of the disease. In the second week the leptospires are difficult to find in the blood; at this time they appear in the urine. However, bacterioscopic examination of the urine in dark-field illumination is just as unpromising as in the blood. An effective method is cultivation of blood specimens obtained within the first 3-4 days of the disease. Should meningeal symptoms appear specimens of the cerebrospinal fluid are cultivated.

A valuable diagnostic method is the inoculation of young guinea pigs (subcutaneous, intravenous, intraperitoneal and intraocular injections) with the blood, urine, and cerebrospinal fluid of suspects.

In addition, there is still another method that has lately proved to be of great practical value in diagnosis. This is the agglutination-lysis test (the lowest diagnostic titre is 1:250) (Fig. 69).

### Prognosis

In spirochetal jaundice the prognosis depends on the form of the disease, and also on the nature of the epidemic. The geographic site of the disease may possibly also play some part (various biological strains of leptospirae produce different clinical courses). Mortality in Japan varies between 11 and 25-40 per cent, in the USA it is 33 per cent, in the Netherlands 12 per cent, in Sweden 15 per cent. According to Gauk, mortality owing to spirochetal jaundice in Europe is 3-4 per cent. Data published in Japanese, American, and Dutch literature give a very high mortality rate for people older than 40 years (63 per cent).

### Treatment

In recent years good therapeutic effects have been obtained with penicillin and biomylin (aureomycin). The previously proposed sulfonamides, bismuth preparations, etc., are of negligible worth.

Penicillin is prescribed in daily doses of 600,000-800,000 u (in 3-4 portions of 200,000 u in 24 hours); biomylin is given three times a day, 0.3 g per dose. The course of treatment is continued until a stable defervescence is attained and the symptoms of the disease disappear. Combined therapy with both preparations is also possible.

The injection of 10-20 ml of a hyperimmune serum at early stages of the disease is recommended by some authors as specific therapy. In severe cases the dosage is increased to 50 ml, and subsequent daily injections of 20-40 ml are given.

Non-specific, symptomatic treatment consists of insulin injections; 10 units are given simultaneously with an infusion of 30-40 ml of 40 per cent glucose. For possible nephritis calcium preparations are recommended: *Calcium gluconicum*,  $\frac{1}{2}$  teaspoonful twice a day; *Sol. Calcii chlorati* 10 per cent, 1 tablespoonful 3-4 times a day.

Nutrition: it is recommended to keep the patient on a light carbohydrate diet and to give him juices and abundant drinks (if the kidneys are not involved).

### Prophylaxis

Prophylaxis resolves into rat extermination and protection of food and water sources against contamination with the urine of rats and farm animals. Human patients are not very important in the dissemination of the infection; however, feces, urine and sputum should be disinfected by flooding with an equal quantity of 10 per cent calcium hypochlorite, 3 per cent chloramine, or 5 per cent lysol.

## MARSH FEVER

Synonyms: water grippo-typhosal leptospirosis (S. I. Tarasov, 1928), epidemic leptospirosis, hay-meadow fever (V. I. Terskikh), water-field fever (Russian); leptospirosis grippo-typhosa (Lat.), Schlammfieber, Erntefieber, Sommergrippe, Feldfieber (Germ.); Charente, leptospirose benigne, fièvre de champs (Fr.); fiebre lagunar (Sp.); slime fever, field fever (Engl.).

### Etiology

Marsh, slime, or field fever is caused by one of the *Leptospira*. Numerous independent serological types have been described. Many *leptospira* types may be isolated simultaneously during an outbreak in one endemic site (V. S. Kiktenko).

The pathogen of marsh fever is *Leptospira grippo-typhosa*, identical with *L. vitulina*; this spirochete stands in close antigen relation to *L. andaman B*.

The organism is pathogenic to man, horned cattle, gophers, rabbits; it is mildly pathogenic to guinea pigs.

### Distribution and epidemiology

Since murine field rodents habitate vast areas marsh fever is observed almost everywhere. At the same time the irregular distribution of endemic sites has been noted both in our country and other lands. This points to the existence of peculiar local conditions favourable to the circulation of the leptospires, physicochemical properties of water and soil, macroclimatic factors, etc. (V. S. Kiktenko, 1954).

Murine rodents are the basic source of infection.

In animals the principal site of concentration of the leptospires are the kidneys. In rodents leptospirosis is not attended by any visible clinical manifestations. *Leptospira*-carriers with no signs of morbidity are observed. In rats the leptospires may be passed with excreta for years (up to 3 years), in mice for several months. A hypothesis has been forwarded by certain authors to the effect that the saprophytic *L. biflexa* that is found in water and soil infests rodents and then acquires pathogenic properties. However, the experimental and epidemiological studies made by Soviet investigators have not confirmed this assumption.

The current point of view regarding the epidemiology of non-icteric leptospirosis is as follows: the leptospires excreted by animals are disseminated in soil and water where they are preserved for a certain time, depending on physico-chemical properties, meteorological conditions, etc. The most favourable conditions for prolonged preservation of the leptospires and their virulence are created in the spring and summer, hence the spring-summer outbreaks of the disease.

The leptospires penetrate into the human body through the alimentary tract, mucous membranes (particularly through lesions in the latter), cracks

and abrasions in the skin, hangnail (leptospires are incapable of penetrating through intact skin). Man usually contracts the infection while bathing in infested lakes or stagnant ponds, or when walking barefoot over boggy soil, flooded meadow-land, rice fields, etc.

### **Clinical aspects**

The clinical features of the different forms of marsh fever are in general the same; the difference lies only in the intensity of certain symptoms, in the longer or shorter duration of the disease, the appearance of insignificant icterus, etc.

The clinical picture has been described by many Soviet investigators since 1927, when V. A. Bashenin observed 411 cases in the Moscow region, and S. I. Tarasov (1928) isolated a culture of its pathogenic agent. The latter was himself subject to an attack of marsh fever contracted experimentally. The case history of Dr. Tarasov gives a most illustrative conception of the clinical course of the disease.

The incubation period of marsh fever varies between 5 and 15 days. The onset of the disease is usually manifested by chills. A high fever (39-40°) continues for 4 to 9 days (in 50 per cent of cases for no longer than 5 days, in solitary cases from 12 to 15 days). Return to normal temperature is gradual, but quite rapid.

Following several apyrexial days a relapse occurs in approximately one-third of cases (a second rise in temperature), a feature quite characteristic of spirochetal diseases. This second pyrexial attack sets in after an interval of 1-2 days, sometimes of 5-7 days, and it is usually short, lasting from several hours to 1-3 days. In very rare cases a third pyrexial attack is observed.

Severe headache is noted from the very onset of the disease (particularly in the back of the head) and muscular pains. In 40 per cent of cases a roseolous eruption appears on the chest, back and extensor surfaces of the arms (in some localities the disease is called "spotted fever" owing to this rash). The incidence of roseolous forms is not uniform in various localities and epidemics.

A well-expressed conjunctivitis is not rare. Jaundice is not typical, but in some cases a subicteric condition of the sclera may be observed for several days (the bilirubin concentration in the blood attains 1-1.5 mg %). The spleen and liver are slightly enlarged. Intestinal disturbances may be noted.

On rare occasions meningeal symptoms are displayed, even a complete picture of cerebrospinal meningitis may be observed, with changes in the fluid. General toxic conditions of the nervous system manifested by insomnia that continues after recovery, and mental disorders have been described.

In the blood a neutrophil leukocytosis is noted, with an increase of band-like and juvenile nuclear forms. Prognosis is usually good, although during intensive outbreaks solitary fatal cases have been registered.

## Diagnosis

An important role in diagnosis is played by epidemiological data (outbreak, association with water bodies, season). For differential diagnosis the disease is compared with malaria, Q fever, typhoid-paratyphoid diseases. Final diagnosis is established by laboratory confirmation, the principles of which are the same as for spirochetal jaundice. Laboratory diagnosis is based on obtaining hemocultures of the leptospire during the first 4-6 days of the disease. The method of direct microscopy is not reliable. According to latest findings, leptospire are voided with human urine, but examination of the urine is not practically effective. Inoculation of guinea pigs is also of no avail owing to the unsusceptibility of these animals to spirochetes of the *L. grippo-typhosa* type.

The most reliable method used in practice is that of serological tests (the antibodies appear on the 5th or 6th day, but it is better to do sero-diagnostic tests on the 9th or 10th day). The reaction is considered positive at a titre of 1:100.

## Treatment

Good effects have of late been reported with penicillin (up to 600,000 u per day until temperature returns to normal). Moreover, a specific hyper-immune serum is also used with good results—up to 20 ml a day. The temperature usually falls to normal in two thirds of cases after the first injection. In some cases repeated injections of serum are required.

## Prophylaxis

The basic measures are extermination of murine rodents and control of epizootic diseases among cattle. In endemic zones it is forbidden to bathe in *Leptospira*-infested water. It goes without saying that rules of personal hygiene should never be neglected, particularly during work on animal farms, etc.

## LEPTOSPIRAL DISEASES OF THE FAR EAST

### Marsh fever FE-A

This disease was observed in the summer of 1933 in the Soviet Far East by S. I. Tarasov (1941), V. S. Kiktenko (1947), E. A. Galperin (1939), and other investigators. It is caused by an independent serological type *Leptospira* FE-A. The clinical features are high fever, severe headache, conjunctivitis, flushed face, albuminuria and lumbar ache. No jaundice is observed. Prognosis is favourable.

Outbreaks of FE-A leptospirosis occur in the hot months of the year in marshy localities. No natural reservoir of the infection is known. In 1940, a strain of the pathogen was isolated from the kidneys of calves that had icterohemoglobinuria (V. I. Tersikh). Guinea pigs are only slightly susceptible to this infection.

### Marsh fever FE-B

Synonyms: type II leptospirosis, Monyakov type (V. I. Terskikh) (Russ.); leptospirosis anictoregenes (A. A. Varfolomeyeva) (Lat.).

The existence of this disease in the Soviet Far East was likewise confirmed by S. I. Tarasov, V. S. Kiktenko and others. The clinical features are absolutely identical to what is observed in marsh fever.

The disease appears in the hot season in persons who bathe in local waters or work in the fields. This strain of leptospires was isolated from sick animals (silver foxes, hogs, horned cattle). It is a serological entity closely related to the *Leptospira* strain discovered on Sumatra.

### Canicola fever

Canicola fever is a disease caused by *Leptospira canicola*. It was discovered in the Soviet Far East. It is also called canine fever. In man it occurs as an intermediate form between spirochetel jaundice and marsh fever (mild jaundice). According to data provided by V. I. Terskikh its clinical course is identical to FE-B marsh fever.

In countries other than the U.S.S.R. (Denmark, the USA) the disease is assumed to be associated with a disease of dogs (Stuttgart disease or canine typhus). In the U.S.S.R. its epidemiology is not clear. The causative leptospire has not been discovered in rodents. Guinea pigs are susceptible to infection; in them it is accompanied by jaundice, and the termination is fatal in 24 per cent of animals.

### ROSTOV INFECTIOUS JAUNDICE

This disease was established in 1938 in the Rostov-on-Don region of the Ukraine (S. Y. Kreitzer, V. I. Terskikh, et al.). The causative agent is a leptospire with serological features closely resembling *Leptospira grippotyphosa* that has possibly acquired independent properties after transformation in horned cattle.

Outbreaks were observed in the summer. Human infection was associated with drinking unboiled water and bathing during a period when spirochetel jaundice was present in horned cattle.

The *clinical aspect* of the disease is more severe than that of ordinary marsh fever. A slight degree of jaundice, as well as an erythematous rash and conjunctivitis, is not rare. The duration of the disease is 8-9 days. Fatal terminations were observed in 4 per cent of cases.

Many independent forms of non-icteric marsh fever have been described in Japan, Indonesia, the Andaman Islands, Italy, etc. We shall point out the most important of them (some have still to be clarified).

### SEVEN-DAY FEVER (NANUKAYAMI)

Synonyms: Japanese leptospirosis, nanukayami (Russ.) leptospirosis hebdomadis (nanukayami) (Lat.); leptospirose du Japon (Fr.).

The pathogen is *L. hebdomadis* (Ido, Ito, Wani, 1918). It is a discrete serological type. Its antigenic properties are close to those of *L. akiyami* B.

*Reservoir of infection:* the field vole *Microtus montebelli*.

The disease is observed in rural areas of Japan (Fukuoka region), in Indonesia, on Taiwan, in Viet-Nam, Thailand, Cambodia.

The *clinical features, treatment and prophylaxis* are the same as in the preceding forms.

### AUTUMNAL FEVER A

Synonyms: Japanese leptospirosis, akiyami (Russ); leptospirosis Akiyami (Lat.); leptospirose du Japon (Fr.).

The pathogen is *Leptospira akiyami* A. It is a discrete serological type. By its antigenic properties it is closely related to *L. autumnalis* and *L. rachmat*. The reservoir of the infection is the field vole *Microtus montebelli* and field mouse *Apodemus specilegus*. The disease is predominantly observed in rural areas of Japan (Schizuoka) and in the Malayan Federation. Outbreaks occur in the autumn.

The *clinical aspects and pathogenesis* are the same as in other forms, but jaundice is more frequent, as are lymphadenopathy and hemorrhage. Fatal terminations occur in 0.5 per cent of cases.

### AUTUMNAL FEVER B

This form differs from the preceding only serologically: *L. akiyami* B possesses an antigenic affinity to *L. hebdomadis*. In natural conditions the reservoir of the infection are *Microtus montebelli* and *Microtus michnoi* field voles.

### HASAMIYAMI LEPTOSPIROSIS

Synonyms: leptospirosis Hasamiyami (Lat.); leptospirose du Japon (Fr.).

Pathogen: *L. autumnalis* (Kaneko, Kotorii, Aoki, 1918).

The pathogen is closely related to *L. akiyami* A and *L. rachmat*. It is very pathogenic to guinea pigs (60 per cent perish with symptoms of jaundice). The natural reservoir is the *Apodemus speciosus* field mouse. The form is widespread in rural areas of Japan (regions of Nagasaki, Hasami, etc.).

The *clinical aspect* of the disease in man is the same as in other forms of leptospirosis, but in 50 per cent of cases jaundice and hemorrhagic symptoms are present. Lethality is 2 per cent.

The Italian forms make up a large group of leptospiroses. The causative agent of *Leptospirosis Poi* is *L. poi* (Mino, 1940). It is observed in the rice fields of Lombardy (Italy).



*Rice leptospirosis* (*Leptospirosis oryzae*) is seen in people working in rice fields in the valley of the Po.

*Leptospirosis Mezzano* affects workers in the rice fields of Pavia.

*Piedmontese leptospirosis* (*Leptospirosis mitis*). The pathogen of this form is *L. mitis* (Mino, 1939). The duration of the disease is up to 8 days. It is seen mostly among those who work in the rice fields of the region of Piedmont (Italy).

## LEPTOSPIRAL DISEASES OF THE TROPICS

*Andaman leptospirosis A* (*Leptospirosis andamanensis*).

Pathogen: *L. andaman A*. (Taylor a. Goyle, 1931). A severe disease accompanied in 30 per cent of cases by symptoms of spirochetal jaundice (icterus, hemorrhages, nephropathy). It occurs in the summer and autumn months on the Andaman Isles.

*Andaman leptospirosis B* (*Leptospirosis andamanensis B*).

The causative agent is *L. andaman B* (Taylor a. Goyle, 1931). The disease corresponds to the ordinary form of non-icteric leptospirosis (marsh fever). It is common to the Andaman Islands and other regions of tropical Asia. Peasants and bathers contract it.

*Batavian leptospirosis* (*Leptospirosis Bataviae*).

Pathogen: *L. bataviae* (Walch, 1926).

The disease is common to Indonesia, and also to southern Europe (Italy). It predominantly affects peasants working in the rice fields. Its clinical features include jaundice and hemorrhages.

*Salinem leptospirosis* (*Leptospirosis Salinem*).

Pathogen: *L. salinem* (Bermann, Mochtar, Essefeld, 1927). A certain part of cases are accompanied by jaundice and hemorrhages. The disease is common to the islands of Sumatra and Java. Murine rodents are the reservoir of the infection.

*Rachmat leptospirosis* (*Leptospirosis Rachmat*).

Pathogen: *L. rachmat* (Vaucel a. Bermann, 1927).

Reservoir: murine rodents. The clinical features are mostly the same as in spirochetal jaundice.

This form of leptospirosis is widespread in Indonesia and Japan.

*Swart van Tienen leptospirosis* (*leptospirosis Swart v. Tienen*).

Pathogen: *L. swart v. tienen* (Walch, 1926). The clinical aspect is that of a severe icterohemorrhagic syndrome. The disease is common to the islands of Java, Kalimantan (Borneo), Sulawesi (Celebes).

*Javanese leptospirosis* (*Leptospirosis javanica*).

Pathogen: *L. javanica*.

The clinical features and epidemiology are little known. The form is common to certain areas of Java.

*Australian Ballico leptospirosis* (*Leptospirosis Ballico*).

Pathogen: *L. ballico* (Cotter a. Sawers, 1934).

*Zanoni leptospirosis* (*Leptospirosis Zanoni*).

Pathogen: *L. zanoni* (Cotter a. Sawers, 1944).



The *clinical aspects* of the disease are the same as in non-icteric leptospirosis (marsh fever). Rodents, chiefly mice are the reservoir of the infection. It occurs during the dry season, after rains (October-February), and also in June-August; mostly observed among labourers on sugar cane plantations.

*Palestine leptospirosis (Leptospirosis Palestinae).*

Pathogen: *L. bovis* (Bernkopf, 1945).

A severe pyrexial disease; jaundice, conjunctivitis, vomiting and muscular pains are not uncommon. Occasionally coma and lethal terminations are seen. Reservoir of the infection: bovine animals, mostly calves, in whom the disease runs a severe septic course. The disease is mostly encountered among the farmers of Jordan, Israel and adjacent areas.

## YAWS (FRAMBESIA)

---

Synonyms: tropical syphilis (Russ.); yaws, framboesia, pian (Engl.); pian (Fr.); boubas, koko, parangi, dube (various languages), etc.

Yaws is a chronic disease characterised by a diversity of skin lesions and, in later stages, of the bones; its clinical features resemble syphilis, but no specific involvement of the internal organs occurs.

### HISTORICAL DATA

The first clinical description of yaws (frambesia) was made in the 16th century by Oviedo.

The causative agent of the disease was discovered in 1905 by Castellani.

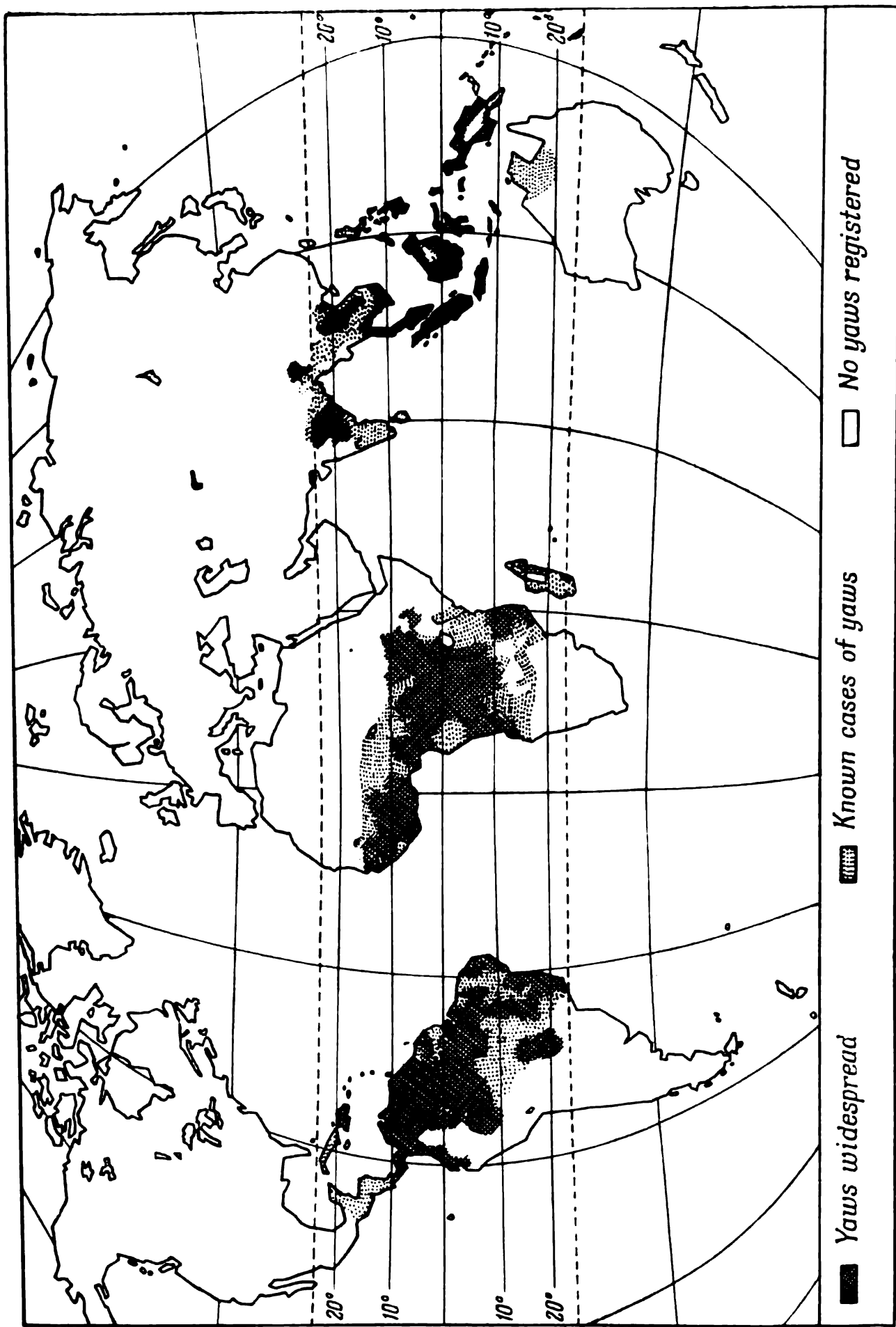
### ETIOLOGY

Yaws is caused by *Treponema pertenue* (Castellani, 1905); the morphological and biological properties of this organism are very close to those of *Treponema pallidum* that causes syphilis.

### EPIDEMIOLOGY

Infection occurs principally through domestic contact, less frequently through sexual intercourse. Outbreaks of yaws in the ore-mines of the South-African Republic have been described. The miners affected by this disease worked in deep shafts where the temperature was 30.5 to 33.5°C. Infection was spread by direct contact of healthy and affected miners working at very close quarters in the narrow mine shafts.

The treponema gain entrance through lesions of the skin and mucous membranes. Possible vectors are flies, particularly *Hippelates pallipes*.



**Fig. 70. Geographical distribution of yaws (frambesia) (Suvanasara a. Hill, 1953)**

## GEOGRAPHICAL DISTRIBUTION

Yaws is a disease of hot climates; it is seen in South America (Guiana, Venezuela, Bolivia, Colombia, Brazil), Central America (Guatemala, Honduras, Costa Rica, Panama), the West Indies (Jamaica, Haiti, Trinidad and other islands), Africa (chiefly on the western coast, in Uganda, Kenya, Tanganyika, the Republic of Congo, and Madagascar); in Asia it has been found in India (Bengal, Travancore and Assam), on Ceylon, in the countries of Indo-China, in southern China, on Taiwan, in Indonesia, North Australia, the islands of the southern Pacific (the Fiji Islands, the New Hebrides, and others) (Fig. 70).

## CLINICAL ASPECTS

The incubation period of yaws varies from 2 to 6 weeks. Its clinical features are greatly diversified.

### International nomenclature of the clinical symptoms of yaws (adopted in 1955).

#### EARLY YAWS

Initial Yaws	(i) papillomatous (ii) ulceropapillomatous
Cutaneous Early Yaws	Macules: erythematous macular early yaws, squamous macular early yaws Maculo-papules: squamous maculo-papular early yaws Papules: simple papular early yaws, umbilicate papular early yaws Micro-papules: acuminate micro-papular early yaws, squamous micro-papular early yaws Plaques of early yaws Nodules: nodular early yaws Papillomata
Mucosal Early Yaws	Mucosal maculo-papular early yaws, mucosal papillomata
Early Yaws of the Palms and Soles	Palmar or plantar papillomata, squamous macular palmar or plantar early yaws Hyperkeratotic macular palmar or plantar early yaws
Early Yaws of the Bones and Joints	Periostitis of early yaws, osteitis of early yaws, osteo-periostitis of early yaws, goundou, sabre tibia, ganglion of early yaws, hydrothrombosis of early yaws
Latent Early Yaws	

## **LATE YAWS**

### **Cutaneous Late Yaws**

#### **Plaques of late yaws**

**Nodules:** nodular late yaws (i) cutaneous, (ii) subcutaneous

**Ulcerated nodular late yaws** (i) superficial, (ii) deep

### **Late Yaws of the Palms and Soles**

**Hyperkeratotic palmar or plantar late yaws**

### **Late Yaws of the Bones and Joints**

**Gummatous periostitis, hypertrophic periostitis of late yaws, gummatous osteo- periostitis, arthritis gangosa, ganglion of late yaws, bursitis**

### **Other Late Yaws**

**Juxta-articular nodules**

### **Latent Late Yaws**

In the prodromal period patients complain of malaise, chills, headache, bone and joint pains in the extremities that intensify by night. The temperature goes up to 37.5-39°; occasionally, particularly in children, diarrhea appears. The first manifestation of the disease is an itching solitary papule, or one or more crops of papules, or an early ulcer. As the papule grows it turns into a granulous papilloma (the “mother yaw”) or fungoid growths of granulations. The granulous papillomas are as a rule noticeably elevated above the surface of the skin. They are covered by a yellow or yellowish-green exudate or crust. Removal of these upper layers reveals raspberry-like\* granulations that bleed easily. The fungoid granulation growths sometimes resemble cancer. They are easily abraded and a watery yellowish exudate that forms crusts seeps out. The initial ulcer is crater-like; contrary to hard chancre of syphilis the base of this lesion is not firm. Initial ulcers are almost always solitary; they bleed easily and discharge a yellow exudate that completely covers their walls. The primary lesions of yaws are as a rule localised on the lower extremities of adults, and on the lips of children. In the absence of treatment these lesions persist for several months or even years together with the later symptoms of the disease. If the lesions heal soon their sites remain visible for some time by a lighter pigmentation of the skin that pass away subsequently. However, scars remain when such lesions have existed for a long time, when they are localised on the face or in the axilla, and when secondary infections occur.

Manifestations of later (secondary and tertiary)† periods of the disease are very manifold. They include papillomatous, macular, papular, desquamative, lupoid, and pigmentative yaws, palm and sole yaws, ulcerative

---

\* Hence the name of the disease “frambesia” — “framboise” means raspberry in French.

† The division of the clinical course of yaws into primary, secondary, and tertiary periods is very conditional and certain authors object to it (Hill, Kodijat, Sardadi, 1951) as the duration of the separate phases of the disease are little known and lesions ascribed to different phases sometimes occur simultaneously.

and gummatous yaws, hyperkeratosis, gangosa, lesions of the bones and joints, juxta-articular nodules.

Papular frambesiform lesions usually develop two years after infection. Their structure resembles the primary lesion of yaws, differing only by the presence of a wide erythematous zone (Fig. 71). These lesions may occur on any part of the body, including the scalp. When radial growth occurs the lesions become ring-like. Lesions localised in moist places

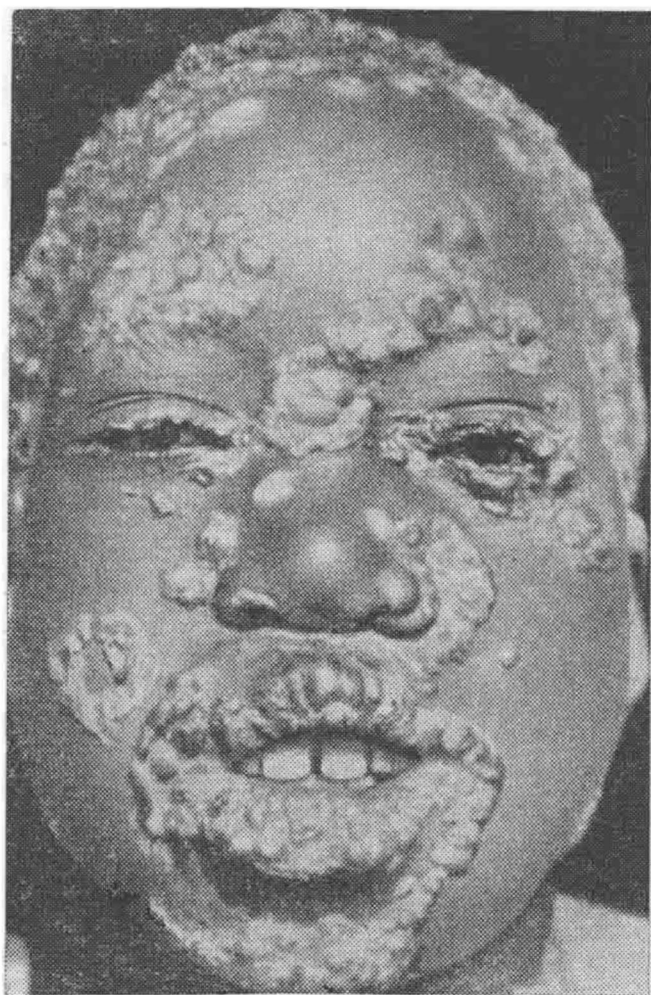


Fig. 71. Yaws. Multiple papillomas (Hill)



Fig. 72. Gangosa and lupoid yaws (Hill)

(around the mouth, nose, vagina, anus, in the armpits) resemble the syphilitic condyloma. The macular yaws lesion is characterised by the presence on the skin of multiple slightly squamous spots approximately 2 cm in diameter that may be either completely depigmented or have a hyperpigmented zone around a pale centre.

Multiple crops of papules cover the entire body or significant parts of it, for instance, the buttocks. These papules look like small lichenoid nodules.

The second type of papules are no larger than a pinhead with an acuminate top covered with a thin crust.

In desquamative forms of lesions there are small or large areas of desquamation on the skin; these areas are covered with powdery ash-grey scales. Papules on the periphery are not uncommon.

Lupoid lesions usually appear several years after primary infection. They are characterised by the formation of granulation tissue terminating in ulceration and atrophy and the formation of mutilating scars (Fig. 72).

Occasionally these scars are hyperplastic elevations (keloids). The diffusion of the process may be of a serpiginous nature, nodules and ulcers appearing on the peripheries, while a scar is formed in the centre of the lesion. In a number of patients no ulceration takes place, and the process terminates with the formation of hyper- or hypopigmented, shiny, wrinkled atrophied areas of skin. Lupoid yaws may cause severe deformities of the body, such as contractures of the joints. The resultant compression of the blood vessels is the cause of necrosis of distal parts of the body, of the toes, for instance, while lymph circulation obstruction leads to elephantiasis.

Pigmented frambesiform lesions are usually formed on the soles and palms, but they may also spread to the dorsal aspects of the extremities. The leukodermic areas so localised are frequently surrounded by zones of hyperpigmented and hyperkeratotic skin.

Lesions of yaws formed on the soles and palms may or may not be accompanied by the formation of extremely painful ulcers.

The non-ulcerative form of yaws on the palms and soles is characterised by the formation of hyperkeratotic areas, erosions, fissures, occasionally eczema. The soles become very painful and the patient is forced to walk with a peculiar gait (trying to step on the outer rim of his feet) that gives rise to the name "crab yaws".

Ulcerative-gummatous lesions of yaws are late symptoms of the disease. Discrete or multiple ulcers form on the sites of cutaneous nodules that break open, and/or from the gumma of the subcutaneous tissues and bones. Development from the primary lesions is rare. The ulcers are usually small and painless, with sharp edges and bright-red granulations. Closure of these ulcers may occasionally result in deformations in the affected areas.

Gangosa (rhinopharyngitis mutilans) is a lesion of the nasopharyngeal structures leading to perforation of the soft and hard palate, severe rhinitis and deformation of the nose. Extensive destructive involvement of the frontal bone with formation of hernia of the brain has been described (Simpson, Eng, Camb, 1938) (Fig. 73). The suffering of the patient is intensified by the combination of gangosa with lesions of the facial skin as, for instance, lupoid lesions (Fig. 72).

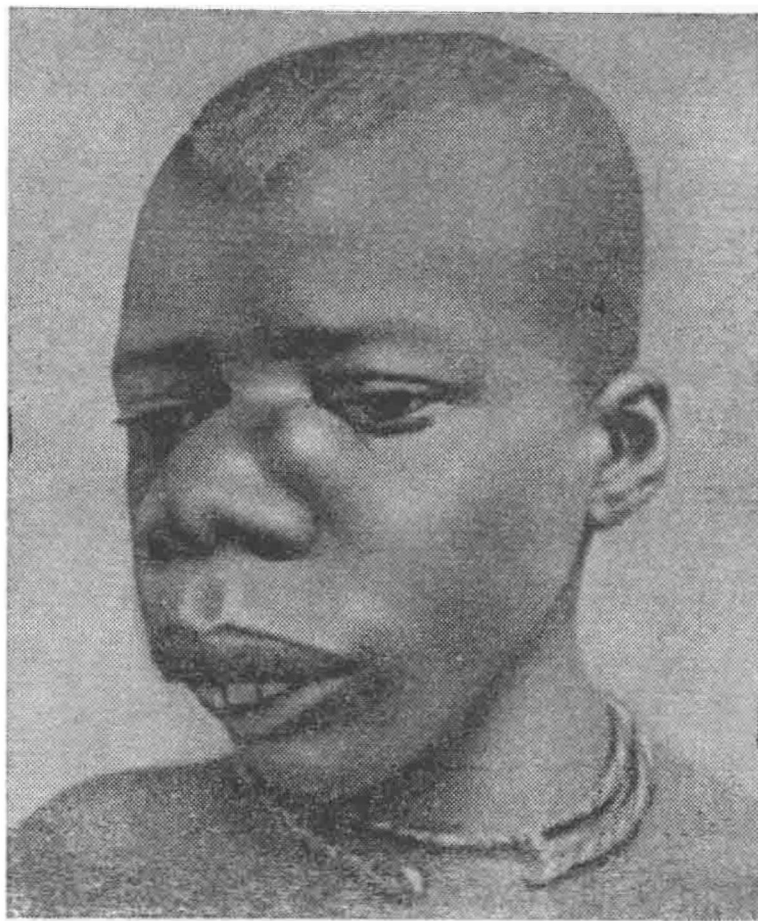
A peculiar form of yaws is goundou. It begins with pain in the head, followed by a hemopurulent exudate from the nose. Symmetric swellings appear at both sides of the bony part of the nose; gradually enlarging, these swellings may attain the size of an orange, or even of an ostrich egg. The mucosal edema leads to constriction of the nostrils. In severe cases hyperostosis of the upper jaw and deformation of the hard palate result (Fig. 74).

Late (tertiary) lesions of yaws include also lesions of the tubular bones in the form of periostitis, osteitis and epiphysitis. These lesions are predominantly formed in the tibia, radius, and phalanges. The result is a deformation of the bones owing to which the tibia, radius and ulna become sabre-like and osteophytes grow on the periosteums of these bones. Occasionally the bones of the hand are affected by lesions of the spina ventosa type.





**Fig. 73. Yaws. Destruction of the frontal and nasal bones; cerebral hernia (Simpson, Eng, Camb)**



**Fig. 74. Goundou (Simpson, Eng, Camb)**



Another symptom attendant on yaws is chronic synovitis of the joints, near which firm fibrous subcutaneous nodules are formed, sometimes the size of a small orange.

Specific lesions of the visceral organs and central nervous system are very uncommon in yaws; indeed, the majority of authors deny their possibility.

## DIAGNOSIS

Diagnosis is established on the basis of clinical findings, laboratory examination of exudates, biopsy of tissues for demonstration of the pathogen, and serological tests. The Wassermann and Kahn tests are frequently positive with blood serum but are, as a rule, negative with cerebrospinal fluid.

### Principal features distinguishing yaws from syphilis (After Manson-Bahr, 1954)

<i>YAWS</i>	<i>SYPHILIS</i>
Not congenital	Congenital
Primary sore—extragenital	Primary sore—usually genital
<i>Secondary Stage</i>	<i>Secondary Stage</i>
a) Typical yaws pathognomonic: furfuraceous desquamation and plantar lesions characteristic	a) Seldom imitates frambesia
b) Mucous membranes not affected	b) Mucous membranes affected
c) Itching common	c) Itching rare
d) Alopecia unknown	d) Alopecia may occur
e) Eyes unaffected	e) Iritis common; choroiditis and retinitis rare
<i>Tertiary Stage</i>	<i>Tertiary Stage</i>
a) Visceral lesions absent	a) Visceral lesions occur, e.g., pericellular cirrhosis, gumma of liver, kidney
b) Nervous system not usually affected	b) Nervous system liable to infection: tabes, G. P. I.
c) C. S. fluid always negative Wassermann	c) C. S. fluid usually positive Wassermann
d) Blood vessels: no endothelial proliferation as in syphilis	d) Endarteritis obliterans of viscera—cerebral thrombosis
Yaws better resisted. Constitutional disturbances slight; great exuberance of eruption and keloid scarring	Syphilis attacks constitution, affecting the vital structures
Does not respond to mercury	Responds well to mercury

## **PATHOLOGY**

The principal sign of yaws is the granuloma. The lesions appear on the skin, in the subcutaneous tissues and bones. Primary and secondary frambesiform lesions are not usually accompanied by the formation of lesions in the deep-lying tissues; such lesions are characteristic of late stages of the disease. At very early stages of yaws a slight thickening of the skin and infiltration of the underlying tissues with lymphocytes and plasma cells are observed. Later papules with thickened epithelium are formed; under these papules granulomatous tissue develops, as well as edema of the corium, and infiltration of the connective tissue with lymphocytes, plasmacytes, and scattered neutrophils and eosinophils. As the infiltration expands the epithelium thins out, tears, and the granulomatous tissue emerges to the surface of the lesions; sometimes ulceration occurs. Hyperkeratosis, edema and degeneration of the epithelium appear on the borders of the lesions. In late stages of yaws the granulomatous process spreads to the deep-lying tissues; this results in the development of fibrous tissue and the appearance of epithelioid cells and occasionally of giant cells. Changes in the bones may be observed during the secondary and tertiary periods of the disease. The principal changes characteristic of the secondary period are diffuse or focal porosities and the development of periostitis with the formation of neoplastic bone tissue. In late (tertiary) yaws the destructive processes in the bones lead to their deformation and the formation of cavities in them.

## **TREATMENT**

Currently yaws (frambesia) is treated, for the most part, with penicillin preparations of prolonged action (bicillin 3, etc.). Levitan, Rodriguez, Jacobs, Petrus, Durand (1953) reported that after one intramuscular injection of 2 ml (600,000 u) of a suspension of procaine penicillin G in oil with 2 per cent aluminum monostearate recovery occurred in all patients with primary yaws and in 90 per cent of patients with later developments of the disease. Persons who came into contact with patients were given prophylactic shots of 300,000 u of penicillin.

However, the committee of experts on venereal diseases and treponematoses recommends 1-2 injections of 1,200,000—1,800,000 u of penicillin for adults.

Hill (1953) has used aureomycin, terramycin, and chloramphenicol with good results. These antibiotics were given perorally for 14 days; the daily dose for adults was 1 g, for children aged between 5 and 10 years 0.5 g, for children younger than five years 0.25 g.

## **PROPHYLAXIS**

To gain control of yaws a planned campaign for revealing cases and treating patients must be carried out; domestic and working conditions must be improved.

# PINTA

---

Pinta (from the Spanish word *pinta*—a spot) is a chronic disease characterised by a peculiar pigmentation of the skin.

## ETIOLOGY

The disease is caused by *Treponema carateum (herrejoni)* (Herrejon, 1927). Morphologically and serologically the organism is closely related to the spirochete of syphilis. The pinta spirochete measures 12-18 microns in length, it is easily impregnated with silver and stained by the Romanovsky technique.

## EPIDEMIOLOGY

The disease is spread by direct contact, and also possibly via bites of midges and bedbugs. Incidence is highest among inhabitants of rural areas and city suburbs.

## GEOGRAPHICAL DISTRIBUTION

Pinta occurs in Mexico, Venezuela, Colombia, Ecuador, Bolivia, and certain parts of Peru, Chile, Guatemala, Honduras, Brazil. It has also been registered in Africa and tropical Asia.

## CLINICAL ASPECTS

In experimental infections of man the incubation period of pinta varies from 7 to 20 days. The initial symptom of the disease is a papule commonly appearing on open parts of the body (following natural infection). The papule slowly increases, turning into an erythematous squamous spot. After some time itching secondary lesions appear on the skin surrounding the primary papule and at some distance from it. Psoriasis-like.

trichophytoid, and lichenoid types are recognised. Hyperpigmentation sets in gradually, later depigmentation in spots of various colour and shape occurs; these spots may be round, ovoid, or irregular in shape, white, pale-blue, lead-coloured, yellow, or black. At late stages of the disease these achromic and pigmented spots are still seen on the skin; palmo-plantar hyperkeratosis and atrophy of the skin develop. The hair on the affected areas turns grey and falls out.

Cardiovascular changes due to pinta (aortitis, aortic aneurysms, valvular lesions) have been described. The possibility of a combination of pinta and syphilis in these cases is not excluded. No tendency of the disease toward cyclic termination has been noted in the absence of treatment.

*Diagnosis* is based on characteristic changes in the skin and the demonstration of the treponema in skin scrapings.

Wassermann test is positive.

*Prophylaxis* has not been evolved.

*Treatment* is effected with neosalvarsan, bismuth preparations, aureomycin (biomycin).

# BEJEL

---

Synonym: endemic syphilis.

Bejel is a chronic disease accompanied by lesions of the skin, the mucous membranes, long tubular bones and nasal bones; these lesions are similar to those produced by syphilis. No specific changes occur in the viscera.

The etiologic agent of the disease is *Treponema bejel*, morphologically undifferentiable from *Treponema pallidum*. The independence of bejel as a nosological entity is doubtful. It is possibly one of the variations of syphilis. The disease is endemic in Arab countries where it has a special affinity for children.

## PROPHYLAXIS

Prophylaxis should be managed by proper treatment of patients, introduction of sanitary measures, improvement of domestic hygiene.

## TREATMENT

Bismuth and penicillin are used for treatment (as for syphilis).

## AMEBIASIS

---

Amebiasis is a protracted parasitic disease prevalently of the large intestine, complicated at times by abscesses of the liver, lungs, etc.

The causative agent of this disease is *Entamoeba histolytica*.

### HISTORICAL DATA

Amebic dysentery has been known for a relatively short time—since the discovery of its causative agent, *Entamoeba histolytica*, by the Russian researcher F. A. Loesch (1875). Although the place occupied by this form of dysentery as compared with the bacillary form is not great, still medical practitioners should be acquainted with it. Amebiasis is encountered everywhere, but predominantly in tropical and subtropical lands.

The furtherance of knowledge on parasitic intestinal diseases, and on amebiasis in particular, is to a great extent associated with the works of Russian scientists. Over a hundred years ago, in 1849, G. Gros discovered an ameba in the human oral cavity that he called *Amoeba gingivalis*. *Lamblia intestinalis* (or *Giardia lamblia*) was first described in Kharkov in 1859 by Lambl. The following protozoans were described in foreign publications: *Trichomonas vaginalis* (Donne, 1837); *Trichomonas hominis* (Davaine, 1860); *Balantidium coli* (Malmsten, 1857). The intestinal ameba (*Entamoeba*/or *Endamoeba*) *coli* was described in 1870 by Lewis and independently of this investigator by Cuninghame (India).

In 1873, F. A. Loesch had under his observation a patient, I. M., a 24-year-old peasant, sick with dysentery. Upon examination of the stool of this patient Dr. Loesch discovered motile formations possessing endo- and ectoplasm and the general characteristic morphology of *E. histolytica*. The description of this organism presented in F. A. Loesch's article leaves no place for doubt.

Loesch called the parasites he had discovered *Amoeba coli* and held that they were the cause of the dysentery. The patient died after having

been ill for over seven months, and was autopsied. The autopsy confirmed both Dr. Loesch's diagnosis and the pathogenic role of the entamebas he had discovered. Loesch infected four dogs with the patient's feces; one of the animals developed acute dysentery.

Since the discovery of F. A. Loesch Russian medical researchers have been making extensive studies of chronic colitis from the view-point of their parasitic origin.

A pupil of Loesch, N. G. Masyutin (Kiev, 1889) described various forms of the dysentery ameba in five colitis patients. The discovery of F. A. Loesch was confirmed by R. Koch who reported finding dysentery amebas in the submucosal layers of the intestines of patients who had succumbed to dysentery in Egypt.

In 1893, Quinke and Roos discovered the cystic stages of the dysentery ameba.

In 1903, the well-known German parasitologist Schaudinn made a strict morphological and biological differentiation between the non-pathogenic *Ent. coli* and the pathogenic *Ent. histolytica*.

In 1904-09, Elmassian described *Entamoeba minuta*.

In 1912, Prowazek made a study of *Entamoeba hartmanni*, a very small ameba of the human intestine that is morphologically similar to *Ent. histolytica* in its cystic stage.

An extremely comprehensive work on amebiasis was carried out in the U.S.S.R. by the prominent parasitologist G. V. Epstein (1914-35). This author, and also Brumpt (1936), Simich and others established that man was an extensive carrier of quadrinucleate cysts.

English and American researchers held that all quadrinucleate cysts belonged to *E. histolytica*, and therefore they contended that the ameba-carriers were very widespread.

Many Soviet authors, while not denying the existence of carriers of pathogenic amebas, singled out the non-pathogenic *Ent. hartmanni* (Prowazek, 1912) and *E. dispar* (Brumpt, 1925).

Subsequently the matter was taken up by leading Soviet parasitologists, A. A. Filipchenko (1933), Y. N. Pavlovsky (1930), V. G. Gnezdilov (1934-56), V. B. Schensnovich (1930-51), L. F. Burova (1927), S. M. Matevosyan (1926-51), D. P. Svanidze (1947-55), A. A. Avakyan (1949-55), and others. The clinical aspect of amebiasis was dealt with most comprehensively by A. N. Kryukov (1921-34).

However, throughout this entire period a certain bias in favour of amebiasis held sway among scientists. The number of carriers of pathogenic amebas, as well as the number of patients, was grossly overestimated (A. A. Filipchenko, 1933; V. G. Gnezdilov, 1934; L. J. Burova, 1934; I. A. Kassirsky, 1934; S. M. Matevosyan, 1951, and others).

The unitary conception of amebiasis that held all quadrinucleate amebas to be etiologically important was subjected to criticism, and currently many Soviet parasitologists are of the opinion that a clear-cut division must be made between *Ent. histolytica typica* and all other quadrinucleate non-pathogenic cysts.

## PARASITOLOGY

The dysentery ameba is *Entamoeba histolytica* (Loesch, 1875; Schaudinn 1903). This ameba belongs to the genus *Entamoeba*, family *Amoebidae*, class *Rhizopoda* (syn. *Sarcodina*). The names *Ent. africana* (Hartmann, 1908), *Ent. nipponica* (Koidzami, 1909), *Loeschia histolytica* (Chatton, 1909), and several others did not take root.

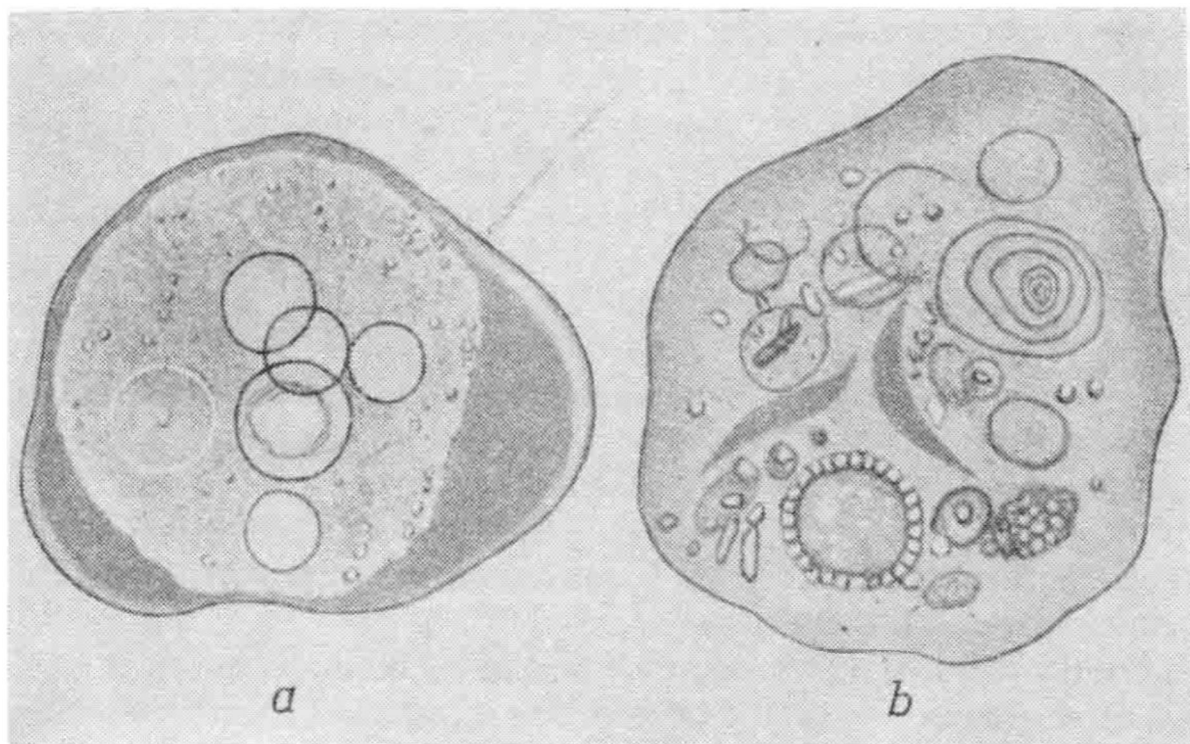


Fig. 75. *E. histolytica* (a) and *E. coli* (b) — vegetative forms

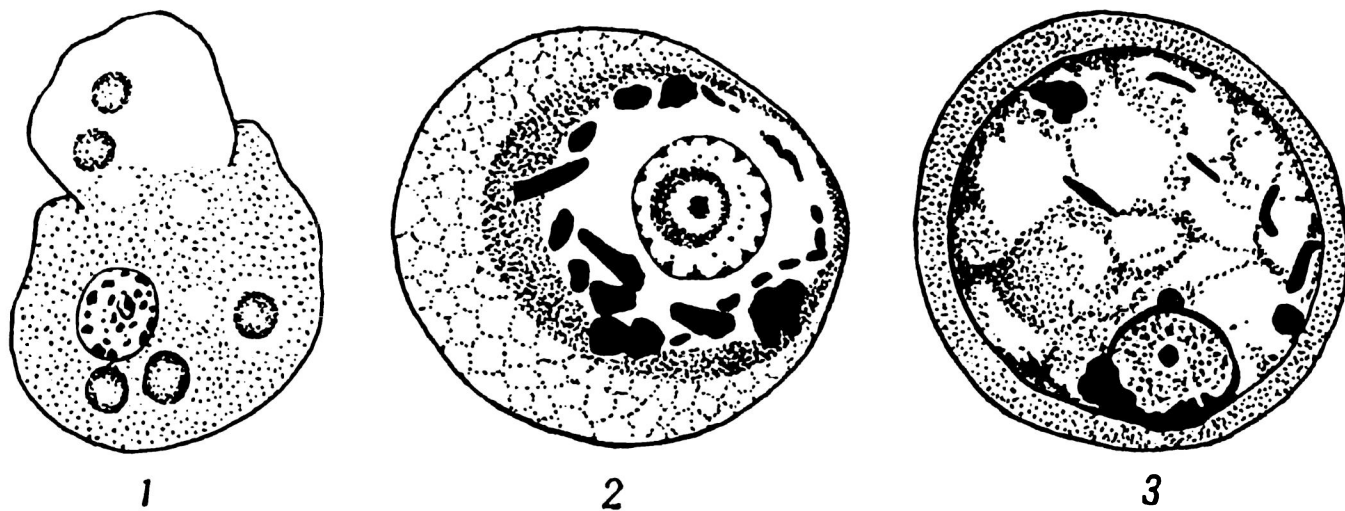


Fig. 76. *Entamoeba histolytica*  
1 — vegetative form; 2, 3 — precystic forms

The dysentery ameba passes through the following developmental forms or stages (D. Svanidze) (Figs 75 and 76):

1. Vegetative tissue form (erythrophage) — *forma magna s. typica*.
2. Vegetative luminal (commensal) form — *forma minuta*.
3. Vegetative precystic (intermediate) form — *forma praecystica*.



4. Cystic (stable) form — *forma cystica*.

5. Vegetative (metacystic) form — *forma metacystica*.

The morphology of *E. histolytica* is studied both in native and stained preparations (iron hematoxylin stain). The diameter of the vegetative form is 15 to 60 microns (on the average 15-25 microns).

In native preparations the vegetative form is characterised by active movement and vigorous formation of wide pseudopodia (lobopodia), the formation of two different aggregate types of protoplasm—the ectoplasm, an outer vitreous layer with no inclusions whatsoever (the pseudopodia are projected from this layer), and the endoplasm, an inner granular layer containing the nucleus, phagocytised erythrocytes appearing as yellowish discs, and some bacteria. The spheric nucleus is clearly visible owing to the refraction of light by the peripheral grains of chromatin underlying the nucleus.

The diameter of the nucleus is 3 to 8 microns. A small karyosome lies in the centre of the nucleus.

*Iodine staining* (with Lugol's solution) provides no special advantages in studying the morphology of the vegetative forms of *E. histolytica*; it appears as in native preparations, the only difference being the absence of motility.

The structural features of the vegetative forms are made clearly visible by staining with iron hematoxylin.

The outer membrane of the nucleus is quite distinct; under it are black clumps of peripherally situated chromatin. A dark karyosome is seen in the centre of the nucleus. The space between the karyosome and the membrane is light-coloured. The erythrocytes are seen as round black formations.

The luminal (commensal) form of *E. histolytica* is *forma minuta*. Many authors hold this form to be the basic biological form of existence of the dysentery ameba (D. P. Svanidze, 1954; V. G. Gnezdilov, 1944; S. M. Matevosyan, 1939, et al.). It appears after the subsidence of the acute process in the intestine and remains for a long time in the upper sections of the large intestine.

The diameter of the luminal form is 15-20 microns, its motility is less marked than in the tissue form. The nucleus is 2.5 microns in diameter; it includes no erythrocytes; bacteria are visible.

Moving along the lumen of the large intestine the luminal ameba penetrates into its lower reaches where conditions for the existence of vegetative forms of the ameba are unfavourable (changes in the pH of the feces and the development of putrefactive processes in the intestine) (V. G. Gnezdilov, 1944). Under these conditions the vegetative form turns into a cyst, passing through the precystic form.

In native preparations the cyst is seen as a transparent, light-refrinent spherical body. The morphological elements are more clearly differentiated when preparations are stained with Lugol's solution. The diameters of the cysts vary from 8 to 16 microns, 12 microns is the average.

The colourless membrane is quite distinct, when treated with iodine it turns brown. Mature cysts contain four nuclei, in immature cysts one,

two, sometimes three nuclei are seen. The chromatin is uniformly distributed under the membrane in small clumps; in the centre of the nucleus there is a small karyosome comprised of one or several granules.

Glycogen-containing vacuoles are seen in immature cysts. A certain number of cysts contain one or several short rod-like, blunt formations, the chromatoid bodies. Together with glycogen these bodies constitute a reserve nutritional supply for the period when the cyst lives out of the body of its host.

*Biology of the dysenteric ameba.* The cysts of the dysenteric ameba are voided with the feces; they are known to be highly resistant to various influences. At room temperature in fecalia they remain viable for up to two weeks. At lower temperatures, particularly temperatures below the freezing point, they can live for several months (A. A. Filipchenko, 1933; V. G. Gnezdilov, 1934). In water cysts keep alive up to eight months; desiccation rapidly destroys them, as do high temperatures (above 60 °C). The number of cysts voided within 24 hours by a patient is, according to Craig, 300 million, while V. B. Schensnovich sets this figure at 600 million. Amebiasis is contracted by ingesting the quadrinucleate cysts. In the intestine these cysts turn into the principal biological form, the luminal ameba, which in its turn transforms into the pathogenic form. This latter form is usually discovered in mucosanguineous stools. It is the opinion of the majority of authors that upon abatement of the pathological process (formed stools) *E. histolytica*, finding itself in normal intestinal surroundings, once again converts into the basic biological form, the luminal form, which subsequently passes into the cystic stage (V. G. Gnezdilov, 1944). The present authors hold that in true amebic dysentery such a strict sequence of stages does not occur, that in all periods the different forms may be found, including *E. histolytica magna*, and that in cyclic or medicinal remissions of the disease only a decrease of the vegetative forms, and not their disappearance, is observed. In a word, we consider that *E. histolytica magna* is an obligatory parasite that cannot exist out of the tissues of a host.

*Short data on the morphology of certain non-pathogenic amebas.* *E. coli* (Grassi, 1879, Casagrandi a. Barbagallo, 1895) is found, on the average, in 40 per cent of subjects examined. The vegetative form has a diameter of 15 to 50 microns, 19-25 microns on the average. The plasma is vacuolised, the ring-shaped nucleus measures 5-10 microns in diameter. The chromatin is distributed under the nuclear membrane in clumps. The nucleus has an eccentric karyosome. Locomotion is characterised by the formation of wide pseudopodia (lobopodia). There are always numerous inclusions in this ameba — microbes, fungi, leukocytes, etc. No erythrocytes are found as a rule. The cysts are round and contain two or eight nuclei, ranging in diameter from 14 to 26 microns, the average being 18 microns. The chromatoid bodies are thin, rod-shaped; in the immature cysts a glycogen vacuole is visible. *E. hartmanni* (Prowazek, 1912) is discovered in 10 per cent of subjects examined. The diameter of the vegetative form is 4 to 12 microns, the diameter of the nucleus measures 2.2 microns. The nuclear struc-

ture is similar to that of *E. histolytica*. Locomotion is very slow. The cysts are spherical; they contain one, two, or four nuclei, and resemble the cysts of the dysenteric ameba; their diameters range from 5 to 10 microns, the average is 7.5 microns. The cysts include a large number of chromatoid bodies and glycogen vacuoles.

EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

The epidemiological aspect of amebiasis has not been sufficiently studied. There are still many obscure questions associated with the conception of the entire parasitological problem of amebiasis.

The incidence of amebiasis is, as a rule, of a sporadic nature. The several epidemic outbreaks described in the U.S.A. and Japan are wide open to doubt, as in all the cases the parasitological diagnosis was far from reliable.

Table 9

World Incidence of Amebiasis

Country	Number of people examined	Percentage of dysenteric amebas discovered	Country	Number of people examined	Percentage of dysenteric amebas discovered
America (North, Central, South):			France .....	1,000	6.5
Canada .....	2,540	9.5	Italy .....	1,600	3
USA .....	114,189	8	Spain .....	2,570	15
Mexico .....	11,428	24	Czechoslovakia ...	440	1.5
Honduras .....	24,871	30	Finland .....	2,114	7
Nicaragua .....	14,860	29	Germany .....	1,000	7.4
Salvador .....	2,215	20	Holland .....	469	10.2
Panama .....	4,473	37	Yugoslavia .....	110	40
Cuba .....	35,255	1.6	Asia:		
Puerto Rico .....	1,474	14	India .....	10,718	13
Dominican Republic	500	14	China .....	1,037	27
Haiti .....	1,275	30	Japan .....	625	9
Guadeloupe .....	7,000	0.2	Korea .....	212	34
Colombia .....	14,767	21	Lebanon .....	1,465	13
Venezuela .....	434	1	Turkey .....	600	12
Ecuador .....	15,410	1.7	Africa:		
Brazil .....	14,926	12	Somali .....	2,500	17
Peru .....	350	23	Ethiopia .....	700	30
Paraguay .....	209	17	Nyasaland .....	832	6
Uruguay .....	2,341	10	Rhodesia, Northern	500	33
Chile .....	3,552	12	Natal .....	105	29
Argentina .....	27,455	13	South Africa .....	22,081	17
Europe:			Guinea .....	90	33
Norway .....	1,111	2	Cape Colony .....	555	10
Britain .....	3,146	3.4	Fernando Po Island	64	30
			New Zealand .....	2,867	3

In general it may be said that amebiasis is a disease observed throughout the world, but is particularly partial to warm lands—the Middle East, India, Indo-China, China, the Philippines, North and Central Africa, the southern states of the U.S.A., Indonesia, and South America.

Poor sanitary conditions in a number of colonial and semicolonial countries have been conducive to a significant spread of this disease, and high figures are still reported on ameba-carriers and morbidity.

There are no official statistics available on the distribution of amebiasis. Table 9 presents the data of Beltria (cited from the work of D. P. Svanidze, 1955).

Amebiasis is encountered in the southern areas of the U.S.S.R. (Central Asia, the Transcaucasus), but even there it is a rare disease, while it is exceedingly uncommon in the northern and temperate zones of the country.

### THE PROBLEM OF AMEBIASIS

The many existing statistical reports (of patchy scientific value and authenticity) seem to make it evident that the percentage of discovered *E. histolytica* and the incidence of amebiasis among the population, particularly of hot countries, is generally high; the version of the vast diffusion of amebiasis is supported by English and American authors. Almost all Soviet scientists formerly also adhered to this point of view (1921-40); a part of the authors still support the old positions. However, to our way of thinking, the history of amebiasis is a history of mistakes. As a matter of self-criticism we must own that a significant portion of these mistakes belonged to us and to the entire school of A. N. Kryukov that first waged enthusiastic over the problem of amebiasis in Central Asia in 1921 and overestimated the weight of this nosological form in the pathology of warm lands.

It is to be regretted that an uncritical view of the teachings on amebiasis has currently been taken by many clinical and hospital institutions; wherefore the importance of amebic invasion in intestinal pathology continues to be exaggerated, a pathogenic role being assigned to a number of histolytic-like amebas that are actually not pathogenic at all, or the importance of the discovery in the feces of quadrinucleate cysts is overestimated.

The authors have made a comprehensive study of the clinical features of amebiasis over a period of 35 years; since the 1930's they have gradually departed from their former opinions.

The reason of the discrepancy between the great percentage of *E. histolytica* discovered and the small number of patients is that diagnosis was based on the demonstration of any cysts with four nuclei, and not only the typical *E. histolytica magna*.

In the attempt to solve this problem several theories have been advanced.

1. *The unitary theory of chronic amebiasis.* The chief proponents of this theory are the American and English protozoologists Craig and Wenyon. They consider that all quadrinucleate cysts, be they the larger ones of *E. histolytica* and *E. dispar* or the smal-

ler ones of *E. hartmanni* (*E. tenius*, *E. minutissima*), are only certain developmental phases of new generations of the dysenteric ameba. According to them the dysenteric ameba cannot live out of its host's tissues; every discovery of amebas in man presupposes infinitesimal anatomic changes in the intestine.

The pathogenicity of the unitary dysenteric ameba changes depending on environment. Under the influence of temperate and northern climates the ameba loses its virulence and evokes either no pathologic symptoms, or only weakly expressed symptoms of chronic colitis. These authors recommend a wide institution of specific therapeutic treatment when quadrinucleate cysts are discovered.

However, this theory is easily routed. One need but consider that a high percentage of quadrinucleate cyst-passers has been discovered in southern zones, in the absence of any intestinal pathology whatsoever in these subjects.

Consequently climate is not the decisive factor in the activation of amebic virulence.

A number of Soviet parasitologists (including V. B. Schensnovich, D. P. Svanidze, V. G. Gnezdilov) hold that the demonstration of luminal forms and cysts can still serve as proof of amebiasis. They consider that invasion with *E. histolytica* does not always lead to the clinical manifestation of amebiasis. In their opinion the dysenteric ameba multiplies in the intestinal lumen in its principal biological form, the luminal ameba, that is not pathogenic to the intestinal wall. As the amebas proceed down the intestinal tract they turn into cysts, as which they are evacuated from the bowels with normally formed feces. Such persons are called *healthy carriers of the dysenteric ameba, or cyst-passers*. This point is quite correct, but it by no means disproves the conception of the present authors on the possible confusion of these cysts with the quadrinucleate cysts of non-pathogenic amebas, and, consequently, on their discovery being insufficient grounds for a final diagnosis of amebiasis. And if to this be added that in all cases of authentic amebiasis the vegetative forms of *E. histolytica* are certain to appear either in artificially induced watery stools or during a cyclic exacerbation of an obliterated form of amebiasis, it then becomes clear that a positive diagnosis of amebiasis can only be established by the demonstration of vegetative forms of the typical dysenteric ameba.

2. *Theory of intensification of virulence of E. histolytica and histolytica-like entamebas by bacterial intestinal infections* (dysenteric bacteria, salmonella, etc). According to this theory bacterial dysentery, coli-enterocolitis (coli-bacillary enterocolitis) so affects the intestinal mucosa that it is easily traumatised, its permeability to amebas increases, and a specific activation of entamebas occurs.

This theory has been substantiated by numerous experimental findings. Highly interesting experiments were carried out by Philipps (1956) who infected guinea pigs raised on sterile food with *E. histolytica* and obtained negative results. However, the addition of various bacteria to the ameba cultures caused amebiasis in other animal experiments (M. Z. Leitman, Stewart, Jons).

Such experiments cannot be ignored. However, this is an entirely different matter: the above authors intensified the virulence of a *pathogenic ameba* by the introduction of a bacterial infection.

We cannot acknowledge the role of the combined infection as interpreted by these authors, for the very simple reason that the most severe cases of absolutely authentic amebic dysentery and abscesses of the liver in the infiltrative phase that we have had occasion to observe were completely responsive to emetine therapy alone. But in cases of chronic ulcerative colitis of a bacillary dysenteric nature (accompanied by the passage of quadrinucleate cysts and *minuta* forms) emetine therapy was constantly unsuccessful, for the trouble was not amebiasis (it did not exist), but the bacterial-dysenteric ulcerative colitis, a condition distinguished by a remarkable resistance to various therapeutic treatment, tenacious course, and tendency to relapses.

3. *Theory of individual susceptibility*. According to this theory the majority of human cyst-passers are unsusceptible to amebiasis, and only solitary persons possess individual susceptibility. However, to admit that thousands of people are not susceptible to amebiasis infection and only a solitary few are would be taking a false position in the conception of the teachings on infections.

The question then arises: can such a parasite be considered pathogenic if it evokes infection in only negligible fractions of a per cent of cases?

4. *Theory based on therapeutic grounds.* There exists a group of clinicians who, upon discovering the cysts of amebic microgenerations in patients with acute or chronic dysentery assiduously treat these patients for amebiasis with emetine, not troubling to do tests for bacterial dysentery. Naturally, in acute cases they obtain "effects", in so far as acute bacterial dysentery rapidly terminates in complete recovery in the majority of cases. But treatment of chronic ulcerative colitis with emetine is either ineffective — they then speak of emetine-resistant amebic dysentery — or else the simultaneous employment of various methods of treatment (diet, regimen, blood transfusion, therapeutic enemas with yatren [chiniofon] productive of good results in bacillary ulcerative colitis) finally lead to temporary relief and healing of the ulcers. However, when early relapses typical of bacillary dysenteric ulcerative colitis do occur these authors are inclined to interpret them as relapses of amebic dysentery, and they commence new series of emetine courses, setting forth prolonged and repeated emetine therapy as a basic postulate in the treatment of amebiasis (G. V. Epstein, L. F. Burova, and others). Such were the general lines on which A. N. Kryukov and his associates worked in Central Asia (1921-34).

Now, when it has already been established that in Central Asia, the Transcaucasus and the hot zone in general, as well as in the north, bacterial dysenteric infections are extremely predominant in the origin of chronic ulcerative colitis a turnabout in the interpretation of the etiology of chronic ulcerative colitis is in the making: amebiasis percentages have become lower in statistical data. A. A. Avakyan, an expert in the problem of amebiasis, emphasises that in a clinical observation of 165 cases of chronic ulcerative colitis he succeeded in discovering only 5 cases of amebiasis, all of them of southern origin.

In numerous repeated scrupulously performed cultures of specimens obtained from children with chronic colitis Y. D. Ravich-Birgher (Moscow, 1947) proved the bacterial dysenteric etiology of chronic ulcerative colitis: a total of 5,396 cultures were prepared with material obtained from 497 patients; in 31.5 per cent of these preparations dysenteric bacilli grew. Similar data have been reported in recent works carried out in Soviet clinics (A. A. Askarov, 1947; G. P. Rudnev, 1955; A. F. Bilibin, 1950; S. I. Ratner, 1953, and others).

What conclusions may then be drawn from what we have discussed?

The number of amebiasis cases is evidently very small and it is necessary to work out some manner of criteria for clinical and parasitological diagnosis in order to clear the "confusion" created in the past in the conception of amebiasis; this confusion has led to the assertion of gigantic numbers of ameba-carriers and has conditioned a too broad diagnosis (even currently) of amebic dysentery, erroneous emetine therapy and unsubstantiated conclusions on emetine-resistant amebic dysentery.

*Basic principles in practical parasitologic diagnosis of amebiasis.* Intestinal amebiasis may occur both in pronounced and blurred (torpid) forms. The proof of the diagnosis of amebic dysentery is the demonstration in the feces, or in mucus obtained by rectoromanoscopy, of the large tissue forms of the dysenteric ameba with erythrocytes included in them. The establishment of the etiological role played by the dysenteric ameba in atypical colitis is frequently associated with considerable difficulty. The discovery of the characteristic ameba in the cystic or luminal forms is still no absolute proof that the given disease is amebic dysentery.

Upon examination of fecal matter major attention should be directed to the presence and contents of mucosanguineous clots. At the active stage of the disease large motile vegetative forms of the dysenteric ameba (tissue forms) are demonstrable in the stool; some of these tissue forms contain

erythrocytes. Upon improvement of the patient's condition luminal forms with no erythrocytes in them, and also cysts, are discovered in the stool. During spontaneous exacerbation of the disease (intestinal disorders) or following the administration of a laxative, the vegetative forms again become demonstrable.

Fecal specimens should be collected in a clean dry vessel. Microscopy must be performed directly following defecation (within 15 minutes). A small clot of mucus is placed on a glass slide, a drop of normal saline solution is added, and a cover glass is placed over the drop. Examination must be very exhaustive (several preparations are studied).

In order to obtain a clearer view of the luminal forms and cysts the preparation is treated with Lugol's solution (iodine). It is likewise desirable to prepare some permanent slides stained with Heidenhain's iron hematoxylin.

The cysts are demonstrable in feces refrigerated for several hours.

Upon the discovery of only quadrinucleate cysts or luminal forms of the amebas the laboratory report must point out that no positive proof of amebic lesion of the intestine provided by the tissue forms of the dysenteric ameba have been discovered.

#### AMEBIASIS CLASSIFICATION

There are many classifications of amebiasis in existence, but the most comprehensive was compiled by D. P. Svanidze (1954). We present this classification as the most circumstantial, but with the reservation that certain forms (e. g., the cutaneous and pulmonary) are very rare.

##### I. *Intestinal amebiasis.*

1. Acute amebiasis of the intestine. Clinical course: a) acute amebic colitis; b) acute amebic dysentery.

2. Chronic (relapsing) amebiasis of the intestine. Clinical course: a) chronic colitis; b) chronic dysentery.

3. Intestinal complications of amebiasis:

- a) amebic perforation with peritonitis;
- b) ameboma, or amebic granuloma (clinically manifested as a tumour of the colon);
- c) amebic appendicitis;
- d) constriction of the intestine (by scars);
- e) prolapsus ani.

4. Latent amebiasis of the intestine (primary latency and intervals between relapses — secondary latency).

II. *Extraintestinal amebiasis.* The clinical features are those of early and late extra-intestinal complications of amebiasis.

1. Amebic hepatitis. Clinical course: a) amebic non-suppurative hepatitis; b) amebic abscesses of the liver.

2. Amebic abscesses of other organs (lungs, brain) are observed for the most part in China and Egypt.

3. Cutaneous amebiasis.



III. *Amebiasis and concomitant diseases* (bacterial dysentery, balantidiasis, helminthic invasions).

The authors of the present work consider it expedient to add to the groups singled out by D. P. Svanidze also meta-amebic (postamebic) colitis (residual irreversible changes), and secondary disturbances caused by concomitant endogenous (intestinal) vitamin deficiencies and hypoproteinemia.

### CLINICAL ASPECTS

The clinical pattern of amebiasis is characterised basically by intestinal involvement, but it produces an extremely variegated picture.

The incubation period is difficult to establish in clinical conditions. In experimental infections of volunteers it varies between 20 and 35 days.

In intestinal amebiasis diarrhea is the cardinal symptom. The onset of this condition is insidious; at first the stool is not frequent (3-4 times); abdominal cramps are noted. The stool is, as a rule, abundant, and diarrheal. Contrary to what is observed in bacterial dysentery, the propulsion of the contents of the small intestine into the large one is not disturbed in amebiasis, therefore the fecal character of the stool is retained throughout the disease.

It was only in very rare cases that the authors saw mucosanguineous stools described by the old authors ("raspberry jelly"). Subsequently the volume of fecal matter diminishes and the stool acquires a more mucinous character. However, mixed courses are more frequent (the stool alternates between diarrheal, mucosal, or colitic). Tenesmus is noted in the acute phase of the disease; later on it is not very marked.

A painful inflammatory stretch in the area of the sigmoid flexure and tenderness in the ileocecal section are detected by palpation.

Gastric secretion is sparsely affected (according to our data anacidity occurs in 11.4 per cent and hypoacidity in 61.3 per cent of neglected cases; in the others the acidity is normal or elevated). The spleen is not enlarged.

The liver usually remains unchanged; however, in cases superimposed by complications acute interstitial hepatitis develops, manifested by enlargement and tenderness of the organ. Liver abscesses are distinguished by quite typical clinical features: a hectic, sometimes high monothermic fever, shivering chills, rapid development of anemia, and a high leukocytosis with neutrophilosis, shift of the granulocyte count to younger forms, and marked toxic granulations in the granulocytes. The extent of liver enlargement depends on the location of the abscess. When the site is in the lower parts, particularly in the left lobe, the liver bulges forward and becomes sharply enlarged downward; the organ is hard and painful. When the site of the abscess is in the cupola and centre of the right lobe the liver expands chiefly upward (this is established by X-ray examination). In these cases the patients complain of pains in the back and under the shoulder blade. In neglected cases perforation of the abscess into the pleural cavity, lungs, abdominal cavity, intestine or some other visceral organ is possible.



Abscesses of the lungs and brains, with corresponding clinical symptoms, are much rarer.

Cardiac involvement is manifested by toxigenous and hypovitaminic signs of dystrophy, correspondingly reflected in the electrocardiogram (diffuse changes). In the intestinal form the blood shows a development of a very moderate anemia and leukocytosis with a slight increase of non-segmented neutrophils during the period of exacerbation. Rectoromanoscopy reveals a mottled picture, ranging from superficial lesions of the mucosa (erosions) to large deep ulcers with undermined edges and uneven sebaceous beds, distributed discretely along the sigmoid and the rectum. Complications: constriction of the intestine, amebomas, perforative peritonitis, gangrene of the large intestine, amebic ulcerative-necrotic processes in the perineum, etc.

### DIFFERENTIAL DIAGNOSIS

The differential diagnosis of amebic and chronic bacterial dysentery is conducted on the basis of the following symptoms.

*Amebic dysentery is characterised by:* 1) a relatively slower development (commonly in the absence of fever) of intestinal symptoms; at the onset an enterocolitic syndrome prevails, gradually turning into a colitic syndrome; 2) the prolonged absence of any marked symptoms of intoxication, emaciation, adynamia; 3) a cyclic development of the pathologic process — alternation of diarrhea with constipation; 4) a characteristic rectoromanoscopic picture (hyperemic mucosa on which deep, undermined, sebaceous-lined ulcers are visible, although in some instances the authors have observed an extremely distinct and widespread inflammation of the mucous membrane, with polyps in some places; 5) involvement of the cecal and sigmoid parts of the intestine; 6) the occasional complication of colitis with an amebic abscess of the liver.

The typical features of bacterial chronic colitis are: 1) an acute onset, usually accompanied by symptoms of proctosigmoiditis that gradually passes into a chronic ulcerative colitis involving the entire large intestine — pancolitis (the direct transition of acute dysentery into the chronic form has been observed on numerous occasions by means of repeated rectoromanoscopic examinations); 2) a more distinct toxicosis and rapid emaciation, onset of adynamia, etc.; 3) a characteristic rectoromanoscopic picture: acute inflammation of the mucosa with superficial or deep ulcers of various sizes and irregular shapes, with spongy edges and mucky, bleeding beds (in chronic ulcerative colitis we attach importance to the “symptom of tampon irritation”: when rubbed slightly with a cotton tampon the mucous membrane bleeds; 4) a more frequent than in amebiasis absence of the positive test with mercury bichloride for nuclealbumins (owing to the inflammation of the intestinal mucosa).

However, we consider that the decisive differential-diagnostic feature is the result of protozoologic examination and of emetine therapy.

In typical cases of amebiasis with a profusion of *E. histolytica typica* in the stool a dramatic change takes place in the general state of the patient following the very first injections: the diarrhea disappears and rapid healing of the ulcers commences. The authors have observed complete recovery following emetine therapy even in cases of abscesses of the liver in the infiltrative stage.

#### **PATHOGENESIS AND PATHOLOGY**

The active vegetative form of the dysenteric ameba, concentrating on the surface of the intestinal mucosa and on the crypts, rapidly multiplies and soon involves the mucosa of the large intestine of its host. The amebas eliminate a proteolytic enzyme leading to vigorous cytolysis conducive to



**Fig. 77. Amebic dysentery.**  
Ulcers in the colon

their penetration through the wall of the large intestine (Wenyon, 1926; V. B. Schensnovich, 1947).

Factors considered conducive to the activation of the pathogenic amebas and their penetration into the mucosa are, among others, lowered resistance of the organism and the addition of an intestinal infection. The mucus eliminated in response to irritation and the products of cellular necrosis block the lumens of the Lieberkuhn glands; then a yellowish

nodule (a microabscess) appears and gradually grows and fuses with another abscess. The abscesses grow deeply into the mucous membrane, attaining the submucosal and muscular layers. The ulcers so typical of intestinal amebiasis are formed as a result of rupture of the abscesses. Vegetative stages of the dysenteric ameba are discovered in the stools of such patients.

The pathogenic amebas, burrowing deep into the mucosa, may even go as far as the muscular and serous coats of the intestine. They can also penetrate into the intestinal vessels and from there, via the portal vein system, into the liver, causing one of the severe complications of amebic dysentery. The cavities of liver abscesses are usually filled with a chocolate-brown pus.

The sites of the ulcers are usually in the cecum, ascending, sigmoid, and rectum portions of the intestine. The edges of these ulcers are slightly elevated and undermined, their beds are sebaceous or slightly necrotic, their diameters vary between 2 and 10 mm. They are usually situated on a somewhat hyperemic area of mucosa (Fig. 77). As the disease progresses the ulcers either heal or deepen. We have occasionally observed perforations with limited peritonitis, or amebomas—tumour-like growths in the lumen of the intestine. Rapidly necrotising ulcers, gangrenous forms of amebiasis with very severe courses, are seen rarely.

## TREATMENT

Specific therapy (emetine, yatren) does not exclude symptomatic therapy. The latter resolves into the administration of bismuth subnitrate, 2 g three times a day, dermatol (bismuth subgallate), 0.5 g three times a day, and rivanol enemas (1 : 1,000); moreover, proper diet is also very important. Blood transfusion is very beneficial for weak patients.

For amebiasis complications specific therapy produces good results only in the absence of irreversible anatomic changes (formation of scar tissue).

Fresh polyps, hepatitis, inflammatory tumours of recent formation are resolved by the action of emetine and yatren.

The best therapeutic agent for the treatment of amebiasis is emetine.

*Emetine* (emetine hydrochloride) is a salt of one of the alkaloids of ipecac, the emetic root. Occurs as a white crystalline bitter powder evoking emesis when taken orally. The powder is freely soluble in water. It is used in the treatment of amebic dysentery. Dose: 0.06-0.08 g daily (1.5-2 ml of a 2 per cent solution twice a day intramuscularly).

One emetine course continues for 7-8 days. For curing fresh amebic dysentery 2-3 courses with 7-day intervals between them are sufficient (the intervals are necessary owing to the cumulative action of the preparation). For protracted forms of the disease it is recommended to administer another 3-4 courses.

The side effects of the treatment are nausea (emetine is eliminated through the gastrointestinal tract), adynamia, muscular pain, decreased arterial pressure and the development of polyneuritis.

However, the hazards of emetine therapy are exaggerated by certain authors. On the basis of 35 years of emetine administration the present authors confidently affirm that when all regulations are adhered to no serious complications occur, and it is only in a few patients that general weakness, weakness and muscular pain in the legs are observed. In one case of obvious overdosage (the patient had been taking emetine for a whole month without interval owing to her doctor's oversight) a very protracted course of emetine encephalitis and polyneuritis was observed; the case terminated in recovery.

In prescribing emetine it must be remembered that the effect is obtained precisely at the time when mild symptoms of toxicosis are manifested (the dividing line between the minimum curative dose and the maximum tolerable dose), and this occurs individually, with daily doses of 0.06 to 0.08 g, within the limits of which the doctor should keep.

Recommended emetine dosages for children: younger than one year 0.005 g; from 1 to 2 years 0.01 g; from 2 to 5 years 0.02 g; from 5 to 9 years 0.03 g; from 9 to 15 years 0.04 g.

A proof of the merit of emetine in the treatment of amebiasis are the following statistics on the mortality rate of amebiasis in a number of countries with hot climates.

Table 10

Amebiasis Lethality Before and After Emetine Therapy

Country	Percentage of Lethal Cases	
	Before emetine therapy	After emetine therapy
Egypt	52 (1911-12)	12 (1912-13)
India (Calcutta)	34.6 (prior to 1913)	0 (after 1913)
Panama	18 (1909)	1.9 (1923)

Having convinced ourselves of the excellent effect of emetine, we consider it superfluous to resort to such preparations as emetine-bismuth iodide, emetine periodate, carbarsone and rivanol. In our opinion, some of them have been overadvertised, as, for instance, rivanol, with which we have obtained no particular effects, others are individually toxic. The addition of iodine and bismuth does not in any way alter the efficiency of the preparation.

Infiltrates (amebomas, abscesses in the infiltrative stage, etc.) respond well to emetine. Good results in amebiasis of the liver are obtained with chloroquine diphosphate, (quinamine or resoquine), given perorally for 2 consecutive days in doses of 1 g daily divided into two portions, and after that 0.5 g daily in 1-2 portions for 2-3 weeks. Yatren is also quite effective in amebiasis.

However, long-term experience has shown that liver tissue liquefaction and very large abscesses, as well as secondary infections established by

bacterioscopy of pus specimens obtained by puncture, require surgical intervention.

Neglected chronic cases of amebiasis call for more vigorous treatment (as many as 5 courses). The authors have grounds for affirming that adequate treatment will cure any case of amebiasis (if generalised dystrophy has not occurred). Protracted forms of amebic dysentery are often of a mixed protozoan and bacterial origin.

• *Yatren*. Synonyms: anajodin, besolmin, chinfoform, chiniofon. A mixture of 7-iodo-8-hydroxyquinoline-5-sulfonic acid, and sodium bicarbonate in a 3:1 ratio, containing 25-26 per cent iodine. The substance occurs as a fine yellow crystalline odourless powder that turns dark upon decomposition (should be kept in dry place in air-tight vessel). It is soluble in 30 parts of water (a fizzing sound is heard as it dissolves owing to the elimination of  $\text{CO}_2$ ). For injections the preparation is dissolved in distilled water, freshly boiled and cooled to 30 °C; such a solution is sterile. If the solution were boiled it would decompose, splitting off iodine. Yatren is given orally or in enemas, and, less frequently, in injections. The adult dose is 0.5 g three times a day. This dose may be gradually increased to 3 g daily. Usually yatren has an aperient effect. In enemas the dosage is 1-2 g per glass of warm water (8-day course with 5- to 7-day interval). Yatren treatment may be combined with emetine injections.

*Aminarson* is a Soviet preparation analogous to the American carbarsone. Contains 28.5 per cent of organic arsenic. Available in 0.25 g tablets and in powder form. A single dose is 0.25 g, a daily dose 0.75 g. Dosages for children: from 1 to 2 years the single dose is 0.1 g, the daily dose 0.3 g; for children of 3 years the daily dose is 0.4 g, for 5-year-olds it is 0.5 g, from 8 to 12 years—0.5-0.75 g.

According to M. D. Mashkovsky dosages (both single and daily) for children are lower than the ones here cited. This author (1954) gives the following single doses of aminarson for children: 6 years—0.08 g; 7 years—0.09 g; 8 years—0.11 g; 9 years—0.12 g; 10 years—0.14 g; 11 years—0.15 g; 12 years—0.16 g; 13 years—0.18 g; 14 years—0.19 g; 15 years—0.2 g. Aminarson is not prescribed for children younger than 6 years.

The preparation is given in two 5-day courses with a 5-day interval between them.

As aminarson is less toxic than osarsol (the Soviet analogue of acetarsone), it has now completely replaced the latter in the treatment of amebiasis.

In rare instances of individual intolerance aminarson evokes mild symptoms of toxicosis: elevated temperature, headache, dermatosis, leukopenia. Intervals in the treatment are imperative for avoiding side effects.

Aureomycin (biomycin) is productive of good results in the treatment of amebiasis. The common dosage is 0.5 g three times a day half an hour before meals. The duration of one course of treatment is 6 days; 3 to 4 courses are administered over 7- to 10-day intervals. Doses for children are 0.025 g/kg.

Aureomycin may be given in combination with emetine.

*Terramycin* is prescribed in 0.25 g tablets, four tablets daily for 10 consecutive days.

*Gramicidin* is recommended in the form of enemas; 100 ml of an 0.08 per cent solution is given on alternate days, a total of 7 enemas (A. I. Baldina, 1949).

### PROPHYLAXIS

No specific prophylaxis against amebiasis has been found to date.

Protection generally resolves to revealing the source of infection and *E. histolytica*-carriers. This necessitates thorough cystological examination of feces in special intestinal disease facilities, as well as prophylactic check-up on healthy persons. Necessary measures are: 1) hospitalisation of patients, observance of proper disposal of their feces; 2) all food must be guarded adequately against contamination with soiled hands of cyst-passers; 3) extermination of the causative agents in the outer surroundings; 4) disinfection of drinking water, food, and domestic objects; 5) observance of rules of individual hygiene (washing hands, toilet neatness, etc.). The best way of disinfecting fecal matter containing cysts of the dysenteric ameba is flooding it with a threefold volume of lysol (1:200).

Bedclothes and body linen soiled with feces are either boiled, or soaked for 3 hours in a 3 per cent solution of lysol.

Water is disinfected by boiling (chlorination does not destroy the cysts).

## CHRONIC ULCERATIVE COLITIS (NON-PROTOZOAN)

---

This group of diseases includes *bacillary and non-specific trophic ulcerative colitis* encountered in all lands; they usually constitute complications of acute bacillary dysentery. However, in hot climates the incidence of chronic ulcerative colitis is much higher, and it is associated not only with acute bacterial dysentery, but also with local food habits, frequency and tenacity of fermentative enterocolitis, and endogenous avitaminosis of hot climates.

### ETIOLOGY

The etiological ties between chronic ulcerative colitis of hot lands (for instance, Central Asia) and bacillary dysentery was first established by I. A. Kassirsky and associates (L. F. Burova, A. A. Askarov, T. H. Hajmitdinov, et al.) in 1932-34. These ties were established bacteriologically by cultivation of dysenteric bacilli from intestinal ulcers, and by serological methods.

Subsequently the interpretation of chronic ulcerative colitis from the position of bacillary-dysenteric etiology became most widespread in Soviet literature (G. P. Rudnev, 1942-55; A. F. Bilibin, 1942-56; S.S. Khalfen, 1947; S. I. Ratner, 1953; A. A. Askarov, 1946; K. V. Bunin, 1958, and others). This theory finds its confirmation in the high percentage of dysenteric bacteria in culture growths in cases of chronic colitis and the extremely low (as has recently been shown) percentage of frank, positively proved cases of protozoan colitis among such patients.

Besides the bacillary origin of chronic ulcerative colitis we must also bear in mind its possible trophic allergenic nature (A. G. Alexeyev, 1937, Wagner, 1957).

Indeed, the high incidence of the complications caused by ulcerative colitis of such diseases as chronic fermentative enterocolitis, sprue, pellagra, alimentary dystrophy, etc., force us to acknowledge the importance in the development of chronic ulcerative colitis not only of the bacterial



factor, but also of exogenous and endogenous alimentary factors (observations of the present authors for 14 years in Central Asia; observations of M. I. Slonim, A. M. Kryukov, M. A. Brener, 1941; A. A. Askarov, 1946; N. I. Ismailov, and of many other authors in the tropics and subtropics). The most salient of these factors are polyavitaminosis, neural trophic dysfunction, and the effect of intensive heat on the autonomic nervous system.

Rectoromanoscopy performed on vast numbers of patients afflicted with chronic fermentative enterocolitis, sprue and pellagra has led the authors to conclude that the greater the severity of the basic disease, the more distinct the pattern of chronic ulcerative colitis.

Generally speaking, practice has shown that the specific reactivity of the organism to bacillary dysentery manifested by the onset of chronic ulcerative colitis prevails among acutely malnourished individuals with vitamin deficiencies. Chronic ulcerative colitis is uncommon among well-nourished people.

### CLINICAL ASPECTS

The clinical features of chronic bacillary and non-specific trophic ulcerative colitis are rather variegated.

The onset of bacillary ulcerative colitis is usually more acute than that of amebic colitis; it is characterised by a frequently passed mucous stool and tenesmus (proctosigmoiditis). Trophic ulcerative colitis usually progresses slowly against a background of chronic fermentative enteritis: the

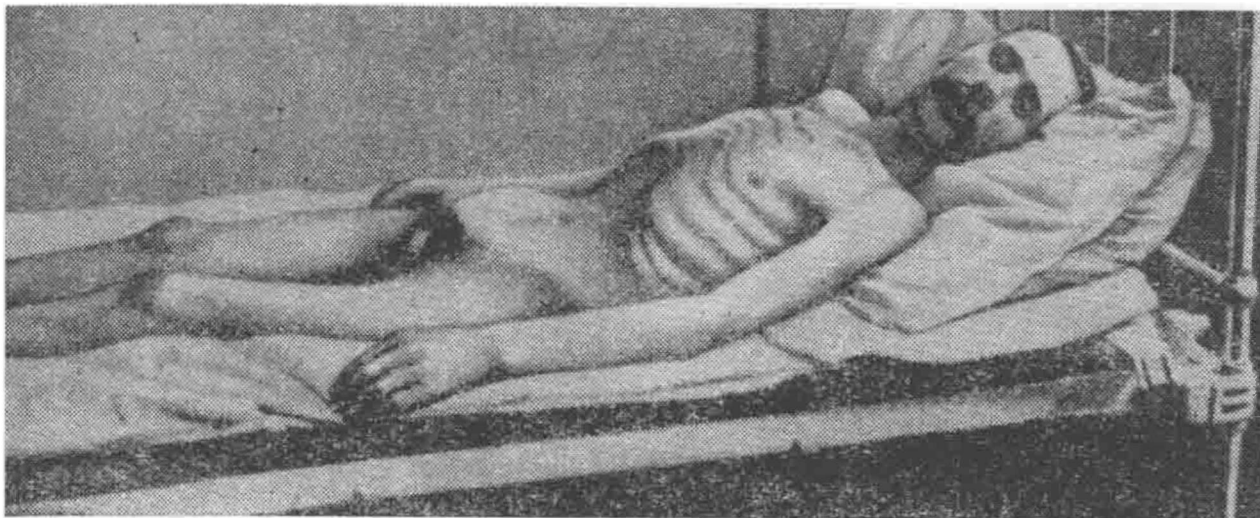


Fig. 79. Emaciation in chronic ulcerative colitis

gradual irritation of the large intestine by the acid intestinal contents cause its mucous membrane to become very tender and easily traumatised, and its permeability to increase greatly owing to alimentary dystrophy and avitaminosis (decreased onkotic pressure in the intestinal tissues).

The syndrome of chronic ulcerative colitis includes colitis (sigmoiditis or pancolitis), progressive debility, progressive emaciation (to the state of cerebro-endocrinic emaciation) and concomitant polyavitaminosis, occasionally subfebrile states and typical inflammatory ulcerative changes in the large intestine as established by rectoromanoscopy (Figs 78 and 79).



The frequency of the stools, tenesmus, mucus and blood in the stools, or prevalence of an enteritic (fermentative) component depend on the nature and severity of the disease. Stools may be voided 3-4 to 10-15 times a day.

The abdomen is usually drawn in, the sigmoid is thickened and painful, in cases of pancolitis tenderness and thickening of the sigmoid flexure



Fig. 80. Ulcerative colitis complicated by pellagra

and the transverse colon are noted. Gastric symptoms most frequently recorded in progressive emaciation are decreased secretion, dyspeptic trouble (poor appetite, putrid eructations, pressure in the substernal area).

Arterial and venous pressure is lowered in such patients, their heart sounds are dulled.

The *blood* shows moderate anemia in cases of frequent blood losses with the stool. The anemia may be disguised by a concentration of the blood. Moderate leukocytosis is uncommon; it is observed only during exacerbations; at this time a moderate increase of younger neutrophil forms is likewise observed. The ESR is slightly accelerated; serological tests show moderate hypoproteinemia with a normal albumin-globulin index. Blood and mucus are usually seen in the form of clots mixed with fecal matter, but in very severe cases large amounts of mucus and purulent masses

accumulate. The feces contain mucus, leukocytes, undigested particles of food, erythrocytes; during exacerbation of the process the mercury chloride test is positive, in markedly expressed fermentative processes the iodophilia test is positive (numerous iodophilic yeast fungi).

*Rectoromanoscopic data:* 1) in the erosive form of chronic ulcerative colitis hyperemia and looseness of the intestinal mucosa, superficial erosions and small ulcers are seen; the mucosa is wounded very easily, the slightest pressure applied with a cotton tampon causes the appearance of mucus and blood in the form of sanguineous drops; 2) in ulcerative forms of moderate severity an acute hyperemia and edema of the intestinal mucosa and in some places erosions and relatively large ulcers are observed; 3) in severe ulcerative colitis the symptoms are acute hyperemia, bleeding, abundant fibrinous and suppurative patches, numerous deep, bleeding ulcers with undermined edges and mucky beds. In a number of cases the authors have observed the development of inflammatory polyposis (the mucosa looks like cobble-stone pavement). The rectoromanoscopic picture changes after treatment has been instituted: the inflammation subsides, secretion of mucus sharply decreases, erosions and ulcers heal.

*Complications.* The complications of chronic ulcerative colitis are constriction of the intestine (the rectoscope cannot pass beyond the site of constriction), pericolitis accompanied by severe pain, liver abscess, interstitial hepatitis, interintestinal abscess, perforation of the ulcer with acute peritonitis and sepsis (most frequently severe coliform or enterococcal sepsis). Besides, progressive emaciation and polyavitaminosis (as in sprue and pellagra) may also develop (Fig. 80).

## TREATMENT

In commencing treatment of chronic ulcerative colitis it is well to remember that intestinal therapy alone is often not enough. The goal should be complex therapy: the general condition of the patient must be improved, the plasma protein and vitamin levels in his body must be restored to normal values; local therapy is also instituted.

Food of full dietary value must be provided, in a form chemically and mechanically tolerated by the intestine. In cases of prevalent fermentative processes in the upper sections of the intestine (the small intestine) a protein-fat diet is prescribed, and digestible carbohydrates are added gradually.

The conception that proteins are contraindicated for colitis as substances evoking putrescent processes in the large intestine is erroneous. Easily digested meat dishes—boiled forced-meat balls, steamed meat patties (quenelles)—are digested in the small intestine and can therefore not serve as material for putrescent processes in the colon. The patient's food must contain all necessary vitamins in abundance (C, B<sub>1</sub>, B<sub>2</sub>, B<sub>6</sub>, B<sub>12</sub>, etc.). Folic acid is also highly recommended (0.05 g twice a day) and vitamin B<sub>12</sub> injections, 100 micrograms twice a week.

The following is prescribed per os:

Rp. Acidi nicotini 0.02  
Calcii carbonici 1.0  
Dermatoli 0.3  
Bismuthi subnitrici 0.5  
M. D. t. d. No. 30  
S. 3 powders a day before meals

Sometimes a good effect is obtained with large doses of bismuth (2 g 3 times a day) and also with sulfathalidine, sulfamethazine, etc.

Beneficial effects are also obtained with regular administrations of *yatren enemas* (1 g per glass of warm water), allowing three 7-enema cycles over one-week intervals (the effect referred to is not an anti-amebic effect, but the usual remedial effect of yatren on the intestinal mucosa manifested in chronic ulcerative colitis).

*Antibiotics* are currently widely employed.

The individual reaction to antibiotic therapy is various.

In some patients the condition responds to levomycetin (levorotatory chloromycetin), in doses of 0.5 g 3-4 times a day on 10 consecutive days, followed by a 5-day interval and a second similar course. In other cases a better effect is obtained with oral administration of streptomycin—0.2 to 0.3 g in a teaspoonful of ecmolin (following the same plan of treatment). Finally, this plan may be applied with biomycin (aureomycin) or terramycin (dosage: 0.3 g 3 times a day).

In mild and moderately severe cases the above measures are completely effective. In very severe cases the treatment should be repeated a month or two later (taking into account the tendency of chronic ulcerative processes to relapses).

In very severe cases it is advisable to perform *blood transfusions* (up to 10 transfusions per course, 150 ml every 5 days).

In the event of the development of sepsis injections of streptomycin, penicillin, and biomycin are prescribed, and terramycin is given orally or by injection.

In recent years many works have been published on the excellent results obtained with corticosteroid hormones in the treatment of chronic ulcerative colitis (prednisone, prednisolone, triamsinolone by mouth, 20-30 mg per day; cortisone injections, 100 mg per day) (Kirsner, Bicks, Palmer; Elliot and Carbone, and other authors).

Surgical intervention is indicated for constriction of the intestine, liver abscess, interintestinal abscess, etc.

In very severe cases accompanied by diffuse ulcers, bleeding polyposis (colitis gravis), in the absence of response to protracted combined treatment, surgery may be recommended—colostomy (cecostomy) with temporary exclusion of the colon, or appendicostomy. Our experience, as well as the data of many authors, have convinced us of the expediency of such operations. Through the surgical opening the intestine is irrigated with solutions of antibiotics, rivanol (1:500), and yatren (1:200). This method, coupled with proper diet and the above-described drug therapy and blood transfusion, yields very favourable results; the condition of

the patient improves, he gains weight, his stool gradually returns to normal, rapid closure of the intestinal ulcers commences, the intestinal mucosa is restored to its normal condition (this is established by rectoromanoscopy).

Reports have been published on good results obtained by resection of the affected portions of the colon.

### **PROPHYLAXIS**

Prophylactic measures against chronic ulcerative colitis in warm lands resolve into control of bacillary dysentery and proper nutrition and treatment of people affected with intestinal diseases.

## SCHISTOSOME DISEASES (SCHISTOSOMIASIS)

---

The synonym for genitourinary and intestinal schistosomiasis is bilharziasis, for schistosomiasis japonica — Katayama disease.

Schistosome diseases are morbid conditions due to helminthic invasion with dioecious trematodes (flukes) of the family *Schistosomatidae* (Looss, 1899). The schistosome diseases most important medically are caused by three species of the genus *Schistosoma* (Weinland, 1858): *Schistosoma haematobium*, *S. mansoni*, and *S. japonicum*. These species of schistosomes live in the blood stream where the females deposit ova that penetrate the walls of the blood vessels and thus emerge into the intestinal tract or urinary bladder from which they are voided with the feces or urine. The propulsion of the ova is facilitated by the fact that the unhatched miracidia (the first larval forms of schistosomes) secrete a peculiar proteolytic substance that is discharged through the egg-shell, displaying a lysic effect on the surrounding tissues. Upon contacting water the ciliated miracidia hatch from the ova; they soon penetrate into the intermediate host — snails. In the snail the flukes go through a series of larval transformations terminating in the formation of caudate larvae — the cercariae. The cercariae leave the body of the snail for the water, where they actively penetrate into the body of their definite host through his skin and mucous membranes; the young flukes (schistosomules) migrate in the host's body and reach the venous system of the abdominal cavity, where they grow and develop to maturity. Schistosomiasis occurs in localities with stagnant water bodies refreshed by underground springs, in slowly flowing rivers and streams, in erratically constructed or managed irrigation ditches, rice fields and similar places favourable to the habitation of snails, the intermediate hosts of blood flukes.

The principal source of snail invasion are schistosome-infested people whose fluke-containing excrements contaminate the water. An essential part in the diffusion of schistosomiasis japonica is played by infested mammals.

The climatic conditions in the southern Philippine islands and on Taiwan are favourable for round-the-year hatching of miracidia. In other sites, for instance, in Japan and Southern China, part of the ova retain their viability through the winter; the miracidia are hatched in the spring.

Man acquires schistosomiasis while bathing and working in contaminated water, and by drinking such water. Chinese authors report that schistosomiasis may be contracted through contact with grass over which infested snails have previously crawled. The incidence of infection is highest among children and individuals whose work is connected with being in water. The importance of unfavourable work conditions may be judged by the fact that among American troops on the Philippines the highest schistosomiasis rate was registered in the military units engaged in building bridges.

The pathogenesis of schistosomiasis is based on toxico-allergic reactions appearing as the result of the emergence into the body of helminthic metabolic and waste products, the mechanical effect on tissues of the migrating larval forms, tissue lysis effected by the enzymes eliminated by the cercariae, schistosomules, and ovum-encapsulated miracidia. In the opinion of a number of authors schistosomiasis creates conditions conducive to the formation of cancer of the visceral organs.

Genitourinary, intestinal, and Japanese forms of schistosomiasis are identified.

### GENITOURINARY SCHISTOSOMIASIS

Genitourinary schistosomiasis is a helminthic condition with prevalent involvement of the genitourinary organs. Synonyms: schistosomiasis haematobia, schistosomal hematuria, urinary bilharziasis.

#### Historical data

In 1851, Bilharz, working in Cairo (Egypt) found a peculiar type of dioecious fluke (existing as males and females) in the mesenteric veins of a human cadaver; these blood flukes were subsequently called *Schistosoma haematobium*. In 1846, Harley proved that the so-called endemic African hematuria was caused by *Schistosoma* parasites. The first morphological study of the schistosomes was made by Looss in 1894. The life history of this fluke was clarified by Leiper in 1915. Treatment of schistosomiasis with antimony preparations was proposed by McDonag (1915), and Christophersen (1918).

#### Etiology

The causative agent of genitourinary schistosomiasis is the trematode (fluke) *Schistosoma haematobium* (Bilharz, 1852; Weinland, 1858).

The male measures from 4 to 15 mm in length and 1 mm in breadth, the female is up to 20 mm long and only 0.25 mm broad. On the celiac surface of the male there is a groove (the gynecophoral canal) in which the female lies. The elongated ova possess a spine or knob (0.12-0.16 by

0.04-0.06 mm) at one of the poles (Fig. 81). This fluke is a parasite of man and apes in its adult stage.

It has been found possible to infect rats and mice experimentally. In its definite host the parasite lodges in the portal vein, the mesenteric veins, and the urinary bladder. Following fertilisation of the ova the worms migrate for oviposition to the capillary vessels of the urinary bladder and

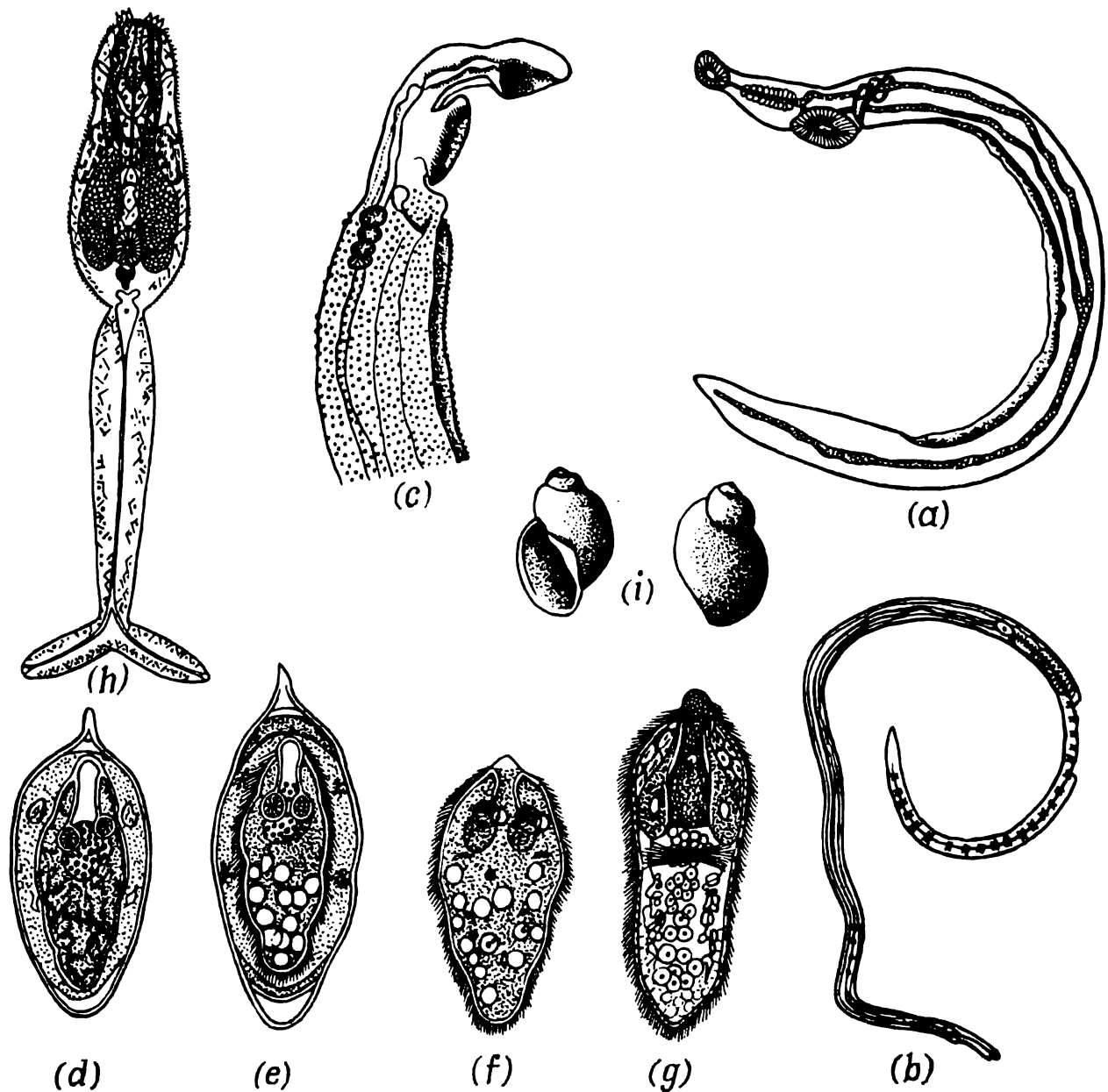


Fig. 81. *Schistosoma haematobium* (Bilharz)

*a*—male; *b*—female (Manson-Bahr and Fairley); *c*—cephalic end of male (Price); *d*, *e*, *f*—ova and miracidium (Railliet); *g*—miracidium (Looss); *h*—cercaria (Bettencourt and Borge); *i*—snail, *Bulinus dybowskyi* (Castellani and Chalmers)

reproductive organs, occasionally also to the intestine. The ova deposited by the female are voided from the body with the urine, and occasionally with the feces. *S. haematobium* lives as long as 26 years, possibly even longer. The intermediate hosts of this parasitic flatworm are various species of fresh-water snails of the genus *Bulinus* (*B. truncatus* and others), *Physopsis* (*Ph. africana globosa*), *Planorbis* (*Pl. medijtensis*, var. *dufour*).

### Geographical distribution

The approximate data computed by Stoll (1947) shows over 39,000,000 people to be infected with genitourinary schistosomiasis. The disease is widespread in a number of African countries—Egypt, Sudan, Uganda, North and South Rhodesia, the Republic of Congo, Angola, the South-

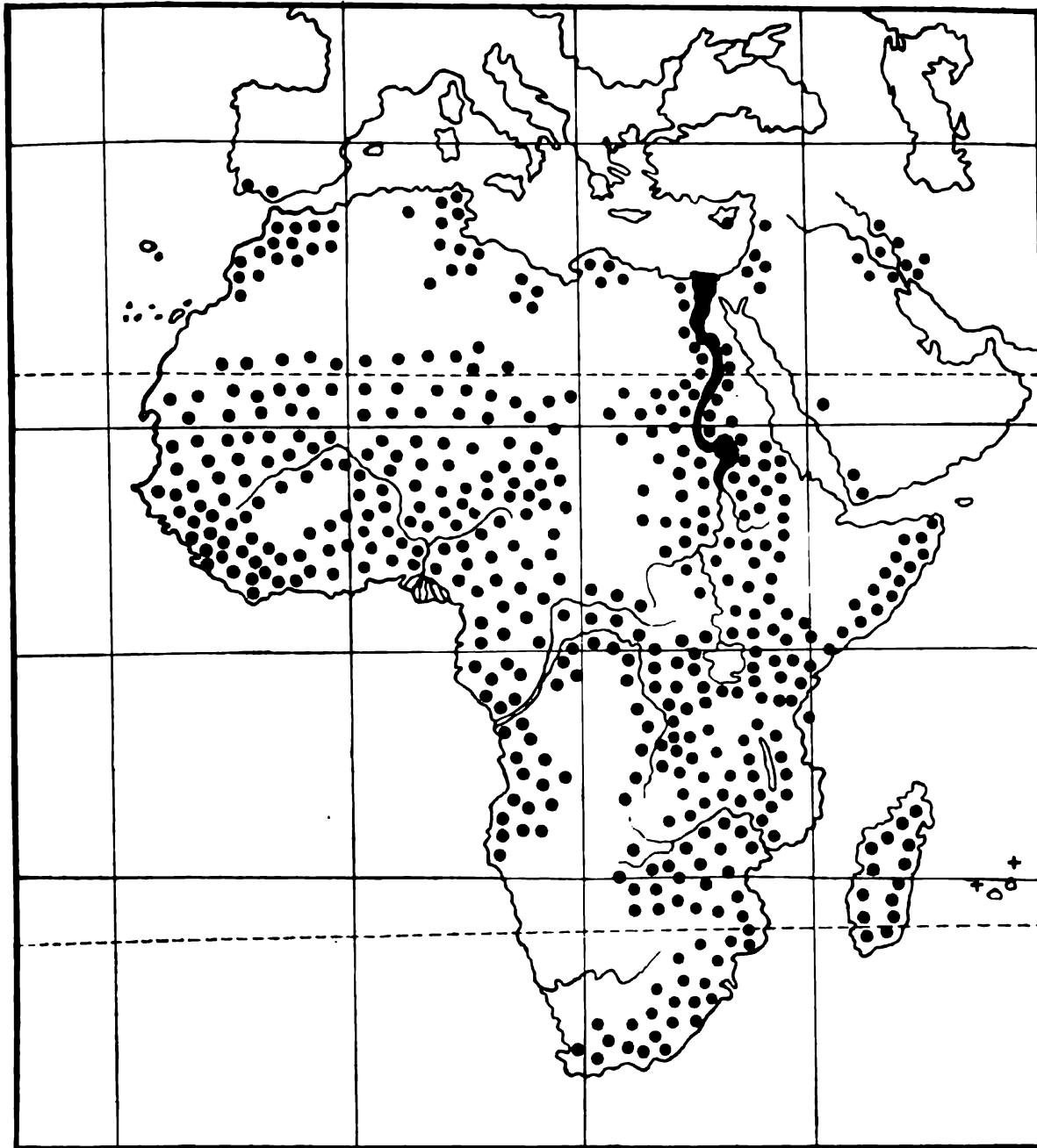


Fig. 82. Geographical distribution of genitourinary schistosomiasis (Faust)

African Republic, Sierra Leone, Cameroon, Gambia; it is very common in Morocco, Algeria, Tunisia. On the eastern coast of Africa its area stretches from Ethiopia to Capeland. The disease is frequently observed in a number of Asiatic countries – Iraq, Syria, Israel, Saudi Arabia, Yemen, Iran; cases have been reported from India. Genitourinary schistosomiasis has been registered on Cyprus, Mauritius, and Madagascar, in Australia, Southern Portugal, Greece (Fig. 82).



In the U.S.S.R. cases of genitourinary schistosomiasis of endemic origin have been described by A.S. Kechek and S. P. Nanasyan (1930), A. I. Mayantz (1931, 1937), and V. A. Aivazyan (1955).

### Clinical aspects

The clinical findings in genitourinary schistosomiasis are very manifold: the course may vary from mitigated forms to very grave ones. At the moment of cercarial penetration under the skin an acute pain is felt, as if caused by a needle. During the period of migration of the parasites in the body allergic symptoms are manifested in the form of fever, itching skin eruptions, eosinophilic infiltrations of the lungs. These early symptoms persist for approximately one month; the next stage is the latent period of the disease, lasting from several weeks to 3 months. When this period ends general weakness, malaise, headache, fever, enlargement of liver and spleen, and eosinophilia in the blood stream ensure. Several months following initial infection the ova of the schistosomes appear in the urine, and symptoms associated with their movement in the tissues are manifested. The earliest sign at this period is the appearance of blood in the urine. The blood is usually discharged in drops at the end of micturition, but in some cases hematuria is observed, with blood present in all the portions of urine.

Endoscopic examination of the urinary bladder at late stages of the disease reveals papillomatous growths on its walls, hemorrhages, ulceration. Later fibrous alterations appear in the bladder tissues, and calcium salts are deposited. Occasionally constriction of the ureteral openings into the bladder may occur, with subsequent development of hydronephrosis, while secondary infection may produce pyonephrosis. The formation of fistulas and urinary calculi in the bladder are possible. Pellegrino and co-workers (1953) examined 23 genitourinary schistosomiasis patients by the method of intravenous pyelography; in 12 of these patients they found structural and functional changes of the urinary system, in 8 patients calculi were present in the bladder walls, in 3 hydronephrosis was registered, in 3 dilatation and calcification of the ureters was observed.

Usborn (1954) examined 100 persons infested with *S. haematobium*; he established the presence of hematuria in 95 patients, dysuria in 84, debility in 5, and abdominal pains in 47 patients.

Acute changes may likewise occur in the reproductive organs of some patients. In males they take the form of epididymitis, prostatitis, vesiculitis, hydrocele. In females the vaginal mucosa coarsens, becoming covered with cracks and polyps; the latter also form on the cervix. Menorrhagia and early amenorrhea are common. In some patients pseudoelephantiasis of the male and female organs occurs. Occasionally genitourinary schistosomiasis is accompanied by intestinal involvement in the form of chronic colitis that may be the principal symptom of the disease, while changes in the urinary bladder take second place or may even be absent altogether.

As a result of migration of the schistosome ova to the liver this organ may be affected by hepatitis with prevalent interstitial involvement.

Pulmonary embolism caused by the ova of the parasite lead to lesions of the parenchyma of the lungs and its arteries. The development of obliterating endarteritis leads to an increase of pressure in the pulmonary artery with subsequent hypertrophy of the right ventricle of the heart. Patients manifest dyspnea, palpitations, dull pain in the area of the heart and the epigastric region, coughing, expectoration of blood. A fatal case has been described wherein the patient succumbed to heart failure due to myocardial involvement as a result of infestation of this organ with schistosome eggs.

In 1952, Zaky described 6 cases of aneurysms of the pulmonary artery caused by schistosomiasis. Faust (1948) cited 8 cases reported by various authors of lesion of the central nervous system as a result of migration of the fluke eggs to the brain and spinal cord. When the eggs lodge in the conjunctiva of the eye yellowish nodules, polypoid formations, and granulomas resembling a chalazion appear in it.

Some authors hold that genitourinary schistosomiasis is conducive to cancer of the urinary bladder. This was also pointed out as far back as 1930 by Brumpt. According to this investigator the combination of genitourinary schistosomiasis and cancer is encountered 11-12 times as frequently as cancer without schistosomiasis. In later years the connection of cancer of the bladder with *S. haematobium* invasion was pointed out by Dejou and Navarranne (1954), and Shamma (1955). The former consider that papillomas of the bladder formed as a result of the schistosome invasion often develop into cancer. In Egypt, where genitourinary schistosomiasis is extremely widespread, the incidence of cancer of the uterus is 11 times higher than in other countries.

### Diagnosis

The diagnosis of genitourinary schistosomiasis is established by clinical findings, laboratory examination of the urine and feces, and immunological tests. The urine is centrifuged, then some non-chlorinated boiled water is added to the sediment. Soon the miracidia hatch out of the eggs; in this case the larvae are easily discerned through a magnifying lens in direct light. A technique for establishing schistosomal lesion of the lungs was recommended by Marques (1952); a sixfold volume of 2 per cent sodium hydroxide is added to the sputum of the patient, this mixture is then warmed until homogenisation takes place, a little water is added, and the mixture is centrifuged for 5-10 minutes at 1,500 rev/min; the sediment is examined for schistosome eggs.

### INTESTINAL SCHISTOSOMIASIS

Synonyms: schistosomiasis mansoni, bilharziasis mansoni, intestinal bilharziasis, bilharzial or schistosomal dysentery.

Intestinal schistosomiasis is a flatworm infestation that prevalently involves the alimentary organs,

## Historical data

In 1903, Manson discovered in the feces of a patient *Schistosoma* eggs with a lateral spike; he stated that in his opinion this must be a third species of trematodes, besides *S. haematobium* and *S. japonicum*, parasitic to man. In 1907, Sambon connected the onset of a dysenteric-like syndrome with the presence in the stools of schistosome eggs with terminal spines; this author proposed naming the then still hypothetic helminth *Schistosoma mansonii*. Cholcomb in 1907 and da Silva in 1909 presented comprehensive descriptions of this parasite, while Leiper clarified its biology in 1916.

## Etiology

The principal agent of intestinal schistosomiasis is *Schistosoma mansonii* (Sambon, 1907). The male measures 10 mm in length by 1.2 mm in breadth, the female is 15 mm long and 0.17 mm broad (Fig. 83). The elongated eggs of the parasite possess a large lateral spine; the dimensions of the eggs are 0.12-0.16 by 0.06-0.07 mm.

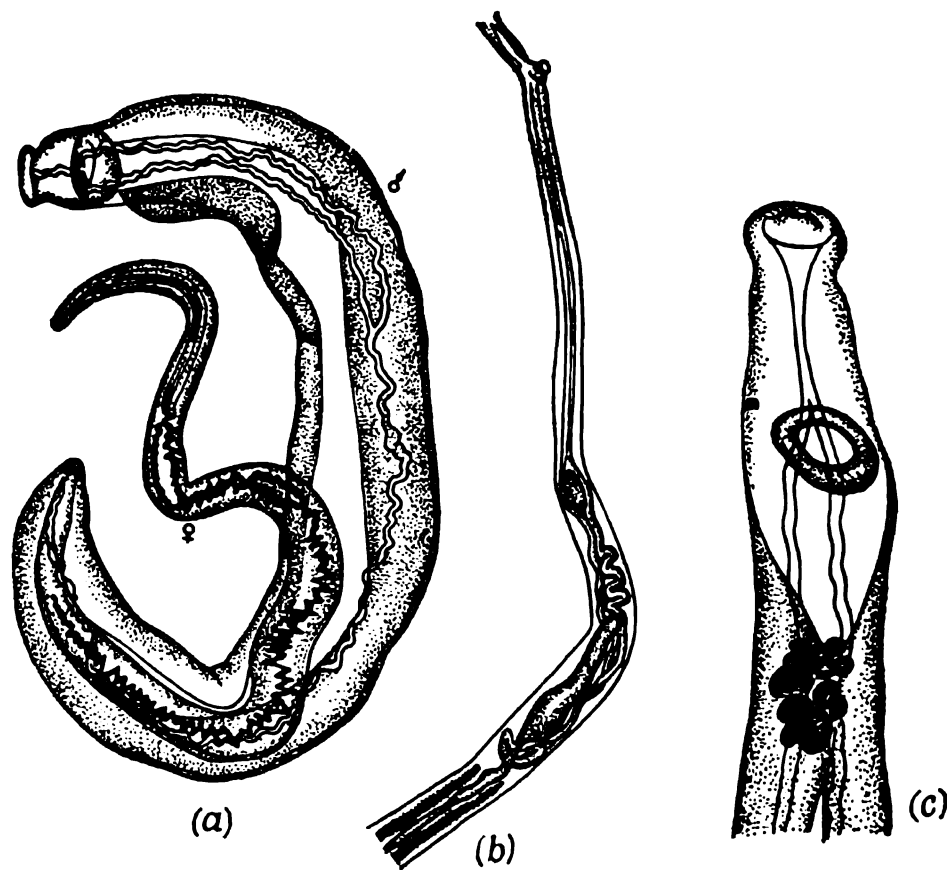


Fig. 83. *Schistosoma mansonii* (Sambon, 1907) (Lutz)  
a—male and female; b—anterior end of female body; c—anterior end of male

At the stage of sexual maturity this schistosome commonly parasitises man, but it has been found in the opossum and in certain species of wild rodents in their natural habitats. The fluke is also capable of attaining sexual maturity in domestic swine.

The female *S. mansoni* deposits her eggs in the small intestinal blood vessels, from whence they emerge into the intestinal lumen and are voided with the feces. Occasionally these eggs are eliminated with the urine. The life-span of these flukes in the human body exceeds 25 years. The intermediate hosts of *S. mansoni* are snails of the genus *Planorbis*, *Physopsis*, *Bulinus*, *Biomphallaria*, *Australorbis*, *Tropicorbis*.

In certain regions of the globe (the Republic of Congo) there is another agent of intestinal schistosomiasis besides *S. mansoni*; this is *S. intercalatum* (Fischei, 1934), the eggs of which possess a terminal shield.

### Geographical distribution

According to Stoll (1947) about 29 million people on earth are infected with intestinal schistosomiasis. The disease is widespread among the population of Egypt, Sudan, the eastern coast of Africa from Zanzibar to

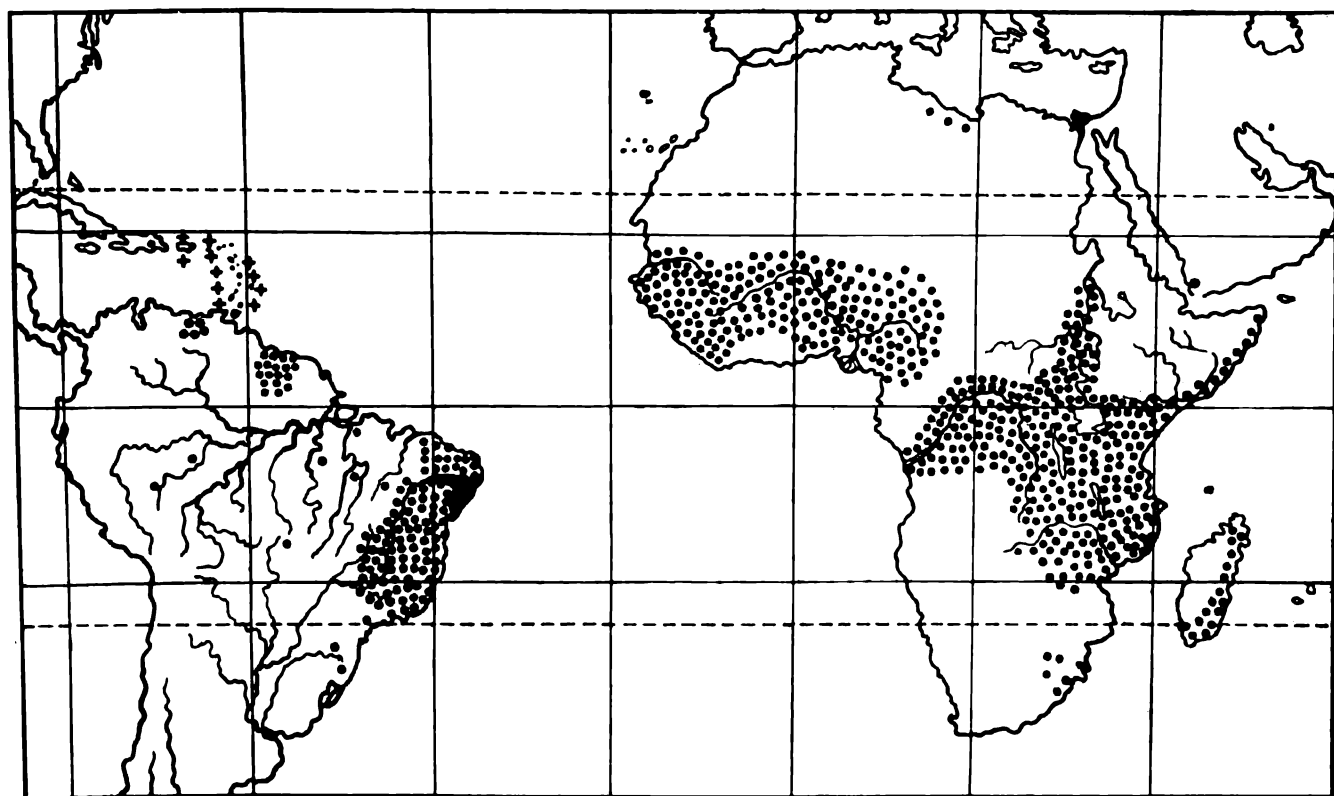


Fig. 84. Geographical distribution of intestinal schistosomiasis (Faust)

the Zambezi river, North Rhodesia, Tanganyika, the Republic of Congo, Guinea, South Cameroon, Liberia, the South-African Republic, Brazil, Venezuela, Puerto Rico (Fig. 84).

### Clinical aspects

In many instances there may be no symptoms of *S. mansoni* infestation; however, severe afflictions and even death are not rare.

The earliest sign of this form of schistosomiasis is a primary dermatitis due to cercarial penetration into the human skin. Allergic symptoms appear on the 5th to 8th day in the form of an intense urticaria, fever,

chills, eosinophil infiltrates in the lungs. Lesions connected with the migration of the ova in the tissues appear 6 to 8 weeks following infection; these lesions are expressed by frequent loose stools, tenesmus, mucus and blood in the feces. Rectoromanoscopic examination reveals hyperemia of the distal section of the intestine, occasionally erosions and small ulcers. The terminal period of the disease is marked by the development of piles, formation of fistulas, prolapsus ani, polyposis of the intestine, mesenteric fibrosis.

Dimmette et al. (1956) point out that polyposis of the sigmoid and rectum is encountered in 17-20 per cent of patients afflicted with intestinal schistosomiasis in Egypt. These authors examined 237 preparations made from benign polyps of the colon resected in surgical operations; in 225 of these preparations they discovered schistosome ova, while of the 98 malignant intestinal tumours examined only 17 were combined with schistosome invasion.

Among the late symptoms of intestinal schistosomiasis are cirrhosis of the liver with splenomegaly and portal hypertension and concomitant ascites and dilatation of the veins of the esophagus and stomach.

Some authors hold that schistosomiasis creates conditions favourable to the formation of primary cancer of the liver. The penetration of the ova into the central nervous system may be the cause of paresis, paralysis, epileptoid convulsions. In the vessels of the pulmonary circulation the parasite is the cause of mural lesions of the arteries and the subsequent development of pulmonary heart. Penetration into the appendix causes appendicitis. Occasionally *S. mansoni* invasion may involve the genitourinary system.

Schistosomiasis may in some cases manifest itself in attenuated, sub-clinical forms. However, these patients are also in need of medical aid and specific treatment, as the disease gradually weakens its victim, rendering him particularly susceptible to other diseases, and shortens his life. Schistosomiasis has a particularly harmful effect on children, inhibiting their physical and mental development.

### **Diagnosis**

Diagnosis of intestinal schistosomiasis is based on thorough clinical and laboratory examinations of the patient. In differential diagnosis the possibility of amebic or bacillary dysentery, balantidiasis, visceral leishmaniasis or malaria must be taken into account. In intensive foci of schistosomiasis its combination with the above-mentioned diseases is quite common.

Ovascopy (microscopic examination for demonstration of ova) is performed in fresh preparations of specimens of the patient's stool. This method is augmented by methods of sedimentation and larvascopy. Sedimentation method: a specimen of the patient's stool is mixed with 250 ml of water, then strained through three layers of gauze into a conic vessel; the vessel is filled to capacity with water. In half an hour the upper layer of liquid is decanted and the vessel is again filled with water. This process

is repeated until the upper layer of the liquid remains clear. The sediment is examined under the microscope. For larvascopy (demonstration of the larvae) the feces are elutriated several times with 2-3 per cent table salt, then centrifuged, and warm boiled water is added to the sediment; the movement of the miracidia that hatch from the eggs is observed by means of a magnifying lens (lateral illumination). Ovascopy is likewise performed in preparations of scrapings and biopsy specimens (the size of a rice grain) of the mucous membrane of the rectum and sigmoid. If liver involvement is suspected specimens obtained by puncture are examined.

During recent years immunological methods of diagnosing schistosomiasis have been widely approved in practice: the allergic skin test and the complement-fixation reaction with antigens obtained from the miracidia, livers of infested snails, cercariae and sex-mature schistosomes.

Valuable data for judging the condition of the distal portion of the colon is obtained by rectoromanoscopy.

### **TREATMENT OF GENTOURINARY AND INTESTINAL SCHISTOSOMIASIS**

Both types of schistosomiasis are predominantly treated with preparations of trivalent antimony, principally tartar emetic (antimony potassium tartrate), antimony sodium tartrate and fuadin. Tartar emetic and antimony sodium tartrate are given only intravenously, in a 1 per cent solution.

Rp. Antimony sodium tartrate 1.0  
Glucose 5.0  
Isotonic sodium chloride solution 100.0  
(Sterilise!)  
DS. For intravenous injection

The solution is infused into the vein very slowly, no faster than 2 ml per minute. Injections are given every day or on alternating days in increasing doses, from 0.03 to 0.1 g of the preparation (3 to 10 ml of the solution) in each injection; the total dosage for one course of treatment for adults is 1-1.5 g of the preparation (100-150 ml of the solution, or approximately 25 mg per kg of weight). The duration of the course is about one month. Treatment is efficient in approximately 90 per cent of cases.

Fuadin (neoantimosan, stibophen), or sodium-antimony-bispyrocatechol-3,5-sodium disulfonate, and an analogous preparation, ripodral, are commercially available in sterile 7 per cent solutions containing 8.5 g of antimony per ml. Injection is intramuscular: the initial dose is 1.5 ml, the next 3.5, and subsequent doses 5 ml per dose. The first three injections are done on consecutive days, the rest on alternating days; the total number of injections for genitourinary schistosomiasis is 10-12, for the intestinal form 12-15. Single doses of fuadin for children are 0.1 ml/kg; the initial injection contains only half of this dose; the duration of the treatment is the same as for adults.

Rp. Fuadini 5.0  
D.t.d. No. 10 in amp.  
S. For intramuscular injections

A preparation closely related to fuadin is fuadin-concentrate; 1 ml of the commercial solution contains 14.3 mg of antimony. A single dose of fuadin-concentrate for intramuscular injections varies from 1 to 3 ml.

Another preparation employed for specific schistosomiasis therapy is anthiomaline (antimony lithium thiomalate); 1 ml of the commercial 6 per cent solution of this substance contains 10 mg of antimony. Helfand (1955) recommends intramuscular or intravenous injections on alternating days, beginning with 1 ml and adding 1 ml to every subsequent injection until the dose becomes 4 ml; this latter amount is administered twice a week until the total anthiomaline dose attains 48 ml.

The prolonged treatment entailed by the above method induced researchers to look for more expedient methods of therapy. In 1945-47 Alves and his associates proposed a method of intensive treatment with antimony sodium tartrate. The course of treatment took only one or two days and consisted of 3-6 intravenous injections of a 1 per cent solution of the preparation, 3 injections per day every three hours; a single dose was 0.06-0.15 g, a daily dose 0.3-0.4 g. The total dose was 0.6-0.8 g to 12 mg per kg of weight (Table 11).

Table 11

Schematic Plan for Treatment of Schistosomiasis  
(after Alves and Blair)

Patient	1st day of treatment			2nd day of treatment			Total dose for cycle
	9 a. m.	noon	3 p. m.	9 a.m.	noon	3 p. m.	
A.	0.12	0.12	0.06	0.12	0.12	0.06	0.6
B.	0.12	0.12	0.15	0.15	0.15	0.12	0.81

Some people manifest a heightened susceptibility to antimony preparations; it is therefore necessary to test the patient's reactivity a few days before administration of the basic treatment by the introduction of a small dose of the drug, e.g., 3 ml of a 1 per cent solution of antimony sodium tartrate is injected and the general condition of the patient is observed. Arterial pressure is measured and an electrocardiogram is advisable. If side effects appear (severe vomiting, collapse, marked ECG changes) intensive antimony treatment is rejected.

In 1947, Alves and Blair reported 97.54 per cent recoveries among 5,455 cases of genitourinary and intestinal schistosomiasis treated by one-day intensive courses of antimony sodium tartrate administration.

Halawani and Abdallan (1946) proposed a modification of the method evolved by Alves; they substituted fuadin for the antimony sodium tartrate, considering the former to be less toxic than the latter. Their patients were given 6 intramuscular injections in two days—3 injections per day over 3-hour intervals. A single dose of the preparation was 5 ml, the total dosage for one course was 30 ml (approximately 0.5 ml/kg).

The intensive introduction of preparations of trivalent antimony has been seen to cause side effects manifested by nausea, vomiting (sometimes very persistent), pains in the joints, feverish chills, decrease of arterial pressure, collapse, and ECG changes due to the negative influence of the drug on the myocardium. Very occasionally papular eruptions on the skin, and shingles (herpes zoster) appear; the present authors have also observed flushed faces. These side effects have been reported to cause death (Barton, 1952). It must, however, be pointed out that the above symptoms may also appear during a routine protracted course of treatment with antimony sodium or potassium tartrates, fuadin or anthiomaline.

Organic diseases of the cardiovascular system, lesions of the liver and spleen unconnected with schistosomiasis, emaciation, and advanced age are contraindications for the prescription of antimonous (trivalent antimony) preparations. Upon the appearance of signs of toxicosis the injections are discontinued and cardiac drugs and glucose are prescribed, for pains in the joints analgin or pyramidon are given, for nausea and vomiting codeine or validol, for the itching caused by shingles an anesthesin ointment is applied, for flushes—dimedrol (benadryl hydrochloride).

During the past ten or fifteen years noteworthy investigations of the effect of miracil D have been carried out. Miracil D is lucanthone hydrochloride 1-(2-diethylaminoethylamino)-4-methylthiaxanthone hydrochloride; it is taken perorally. To mitigate the irritating effect of the preparation on the stomach mucosa the drug is dispensed in tablets coated with a protective substance. In this form the drug is called nilodin (lucanthone).

There is still no consensus of opinion on the most expedient method for the administration of miracil, nor on its efficiency in the treatment of genitourinary and intestinal schistosomiasis.

Alves (1949, 1950) prescribed miracil in powders for patients with genitourinary schistosomiasis for 3-5 days; the daily doses were 15-20 mg/kg (absolute adult doses 0.9-1.2 g), the total dose for one complete course being approximately 60-100 mg/kg (absolute adult dose reaches 3.5-6 g). This author reports cures in 60 to 100 per cent of his cases. With the coated tablets (nilodin) the efficiency of the treatment was only 40 per cent.

Newsome and Halawani (1950) gave their patients 1 g of miracil twice a day for three days; in heavy infections they obtained good results only after the administration of 2-3 courses of treatment over one-month intervals.

Certain authors (Lipparoni, 1953, and others) state that the efficiency of miracil treatment for genitourinary schistosomiasis is no greater than 30-50 per cent. Halawani et al. (1949-1955), holding that short-term treatment with miracil is ineffective, recommend its administration for 18-20 days, prescribing daily doses of 10 mg/kg (for adults the absolute dose is 0.5-0.6 g). These authors report that 80 per cent of their patients were cured by this method.

Contradictory reports have been made by various authors on the efficiency of miracil therapy for intestinal schistosomiasis as well.



The side effects of miracil D are manifested by debility, loss of appetite extending to complete anorexia, nausea, vomiting, abdominal pains, diarrhea, dizziness, headache, yellowish tinge of the skin, increase or decrease of arterial pressure, occasionally inversion of the T wave in the ECG. In some cases the side effects make further treatment impossible.

The efficiency of specific methods of therapy for schistosomiasis is established by thorough clinical and helminthological examinations of the patient for at least several months. Short-time observation may lead to erroneous conclusions, as various preparations cause temporary cessation of oviposition, but not the destruction of the parasites. Therapy results may also be checked by serological tests, the reactions to which become, as a rule, negative three months after complete recovery.

Specific therapy in severe forms of schistosomiasis should be combined with pathogenetic and symptomatic treatment. Thus, Jackson (1956) states that about one per cent of intestinal schistosomiasis patients require treatment for cirrhosis of the liver, thrombosis of the splenic vein, polyposis, intestinal strictures and fistulas. For cirrhosis of the liver Jackson recommends splenectomy and surgical anastomosis between the inferior vena cava and the portal vein. Signal benefit may be obtained in the treatment of cirrhosis by conservative therapy—campolon, antianemin or vitamin B<sub>12</sub>, lipocain, methionine, and large dosages of ascorbic acid.

## SCHISTOSOMIASIS JAPONICA

Japanese schistosomiasis (Katayama disease) is a chronic ailment characterised by predominant involvement of the alimentary system.

### Historical data

The clinical features of this disease were known long before its pathogen was discovered by Fuji (1843) and other researchers. The parasite was first described in 1904 by Katsurada. Its biological principles were established by Miyagawa (1912) and Miyaira (1913, 1914).

### Etiology

The pathogen is *Schistosoma japonicum* (Katsurada, 1904) (Fig. 85). The male measures 9.5-17.8 by 0.55-0.97 mm, the female 15-20 mm by 0.31-0.36 mm. The elongated ova are 0.074-0.106 by 0.06-0.08 mm; they possess a small hooked or rudimentary lateral spine. The adult flukes parasitise the portal and mesenteric veins of man and of a number of mammals—cattle, swine, dogs, cats, rats, mice, monkeys, etc. It is quite probable that *S. japonicum* can live in all mammals. The intermediate hosts of the Japanese schistosome are fresh-water molluscs of the genus *Oncomelania*.

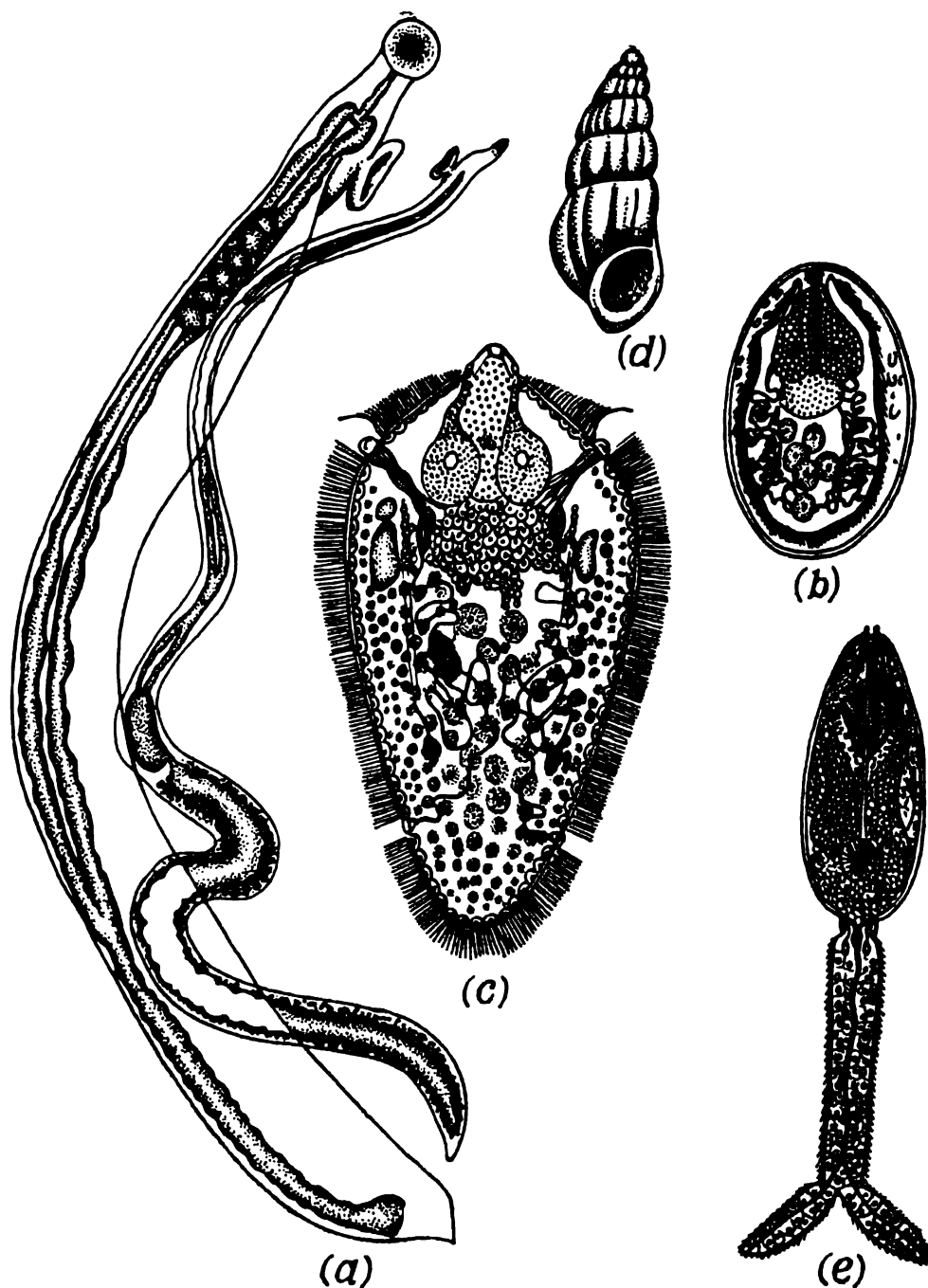


Fig. 85. *Schistosoma japonicum* (Katsurada, 1904)

*a*—male and female; *b*—egg; *c*—miracidium; *d*—snail *Oncomelania*; *e*—cercaria

### Geographical distribution

Japanese schistosomiasis is common to South China and Taiwan, the Philippines, South Japan; it has been registered on Sulawesi (Celebes).

In the Chinese People's Republic schistosomiasis is extremely widespread among the population of the Yangtze basin. Endemic foci have been registered in the provinces Kiang Si, Kiang Su, Szechwan, Ho Nan, Hu Peh, Che Kiang, Fu Kien, Kwang Tung, Yun Nan, An Hwei, and on Taiwan (Fig. 86).

The principal site of Japanese schistosomiasis on the Philippines is Leyte Island; smaller sites exist on the islands Mindanao, Mindoro, and others.

In Japan the sites of schistosomiasis are located in the provinces Chiba, Ibaraki, Yamanashi, Shizuoka, Hiroshima, Okayama, Saga, and Fukuoka. The disease is particularly widespread in the Yamanashi province and on Kyushu (Saga and Fukuoka provinces).

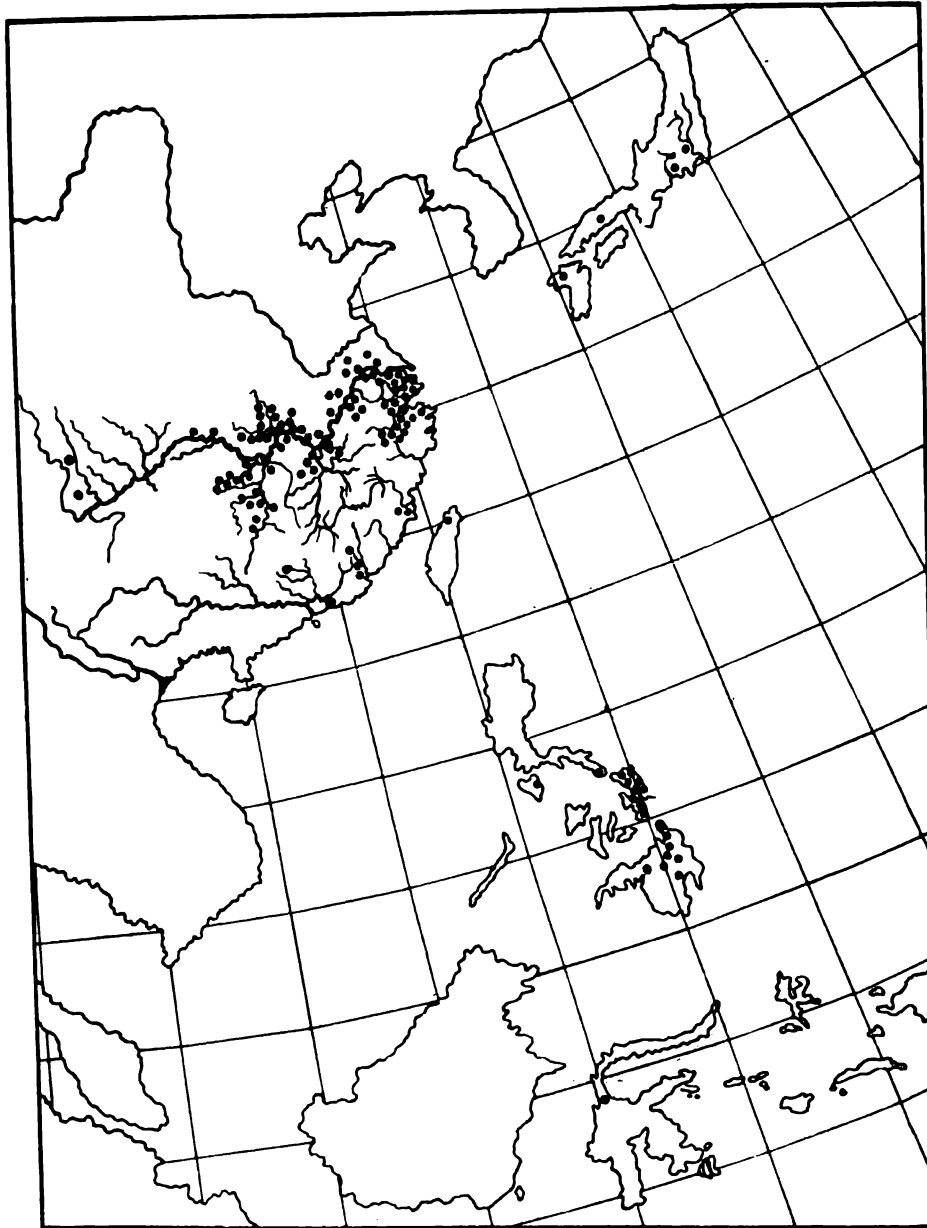


Fig. 86. Geographical distribution of Japanese schistosomiasis (Faust)

### Clinical aspects

Three stages are differentiated in the clinical course of Japanese schistosomiasis: the initial, acute and chronic. The initial stage of the disease is associated with the invasion of the human body by cercarial larvae and the migration of the young helminths (the schistosomules). The first signs of schistosomiasis are shooting pain in the site of penetration of the cercarial larvae and papular or pustular eruptions on the skin. After one or several days feverish chills and a cough appear, also eosinophil infiltration of the lungs, and occasional abdominal pains. These symptoms persist for several days, after which they subside or may even temporarily

disappear; however, in 2-4 weeks (sometimes later) the patient's appetite deteriorates, he loses weight, develops headache and a remittent fever, a heaviness is felt in the epigastric area; the blood shows leukocytosis and eosinophilia. Four to five weeks after infection the stool may become frequent and contain mucus and blood, at times the liver and spleen enlarge. The clinical features of the disease in this phase may vary greatly. Fulminant forms terminating in rapid death have been described, as have severe forms; at the same time attenuated and asymptomatic forms are also known.

In the late stages of the disease constipation is replaced by loose stools of a dysenteric type and schistosomatous appendicitis is fairly frequent; rectoromanoscopic examination shows the presence of polyps, small ulcers, mucosal hypertrophy, and strictures in the distal section of the intestine; prolapsus ani may occur. Anemia is registered in the blood. Cirrhosis of the liver with splenomegaly and ascites is not rare.

The physical and mental development of children and adolescents afflicted with schistosomiasis is retarded as compared with their healthy coevals. Sterility is occasionally noted in women.

Certain authors hold that the hyperplasia of the intestinal mucosa associated with Japanese schistosomiasis is conducive to the development of cancer.

A severe complication of Japanese schistosomiasis is lesion of the central nervous system owing to penetration of the ova into the brain. This may result in paresis and paralysis of the extremities, diffuse encephalitis, meningoencephalitis or meningitis, a brain tumour-simulating syndrome (persistent headache, vomiting, disorders of vision, focal epilepsy). Forty-five cases of this type were described from 1889 through 1947 (Faust, 1948). Nervous system lesions may be observed 4 to 22 weeks after infestation has occurred, occasionally also after two to four years of an asymptomatic course of the disease. In rare cases the ova of the *S. japonicum* penetrate into the myocardium, the skin and lungs. In the latter event X-ray examination shows changes in the lungs resembling lesions typical of miliary tuberculosis.

### Diagnosis

Diagnosis of Japanese schistosomiasis is conducted along the same lines as diagnosis of intestinal schistosomiasis.

### Treatment

Treatment of Japanese schistosomiasis, instituted on a wide scale in the Chinese People's Republic, is carried out almost exclusively with preparations of trivalent antimony (antimonous preparations). Miracil D is absolutely ineffective in this type of schistosomiasis. In China the prevailing preparation is tartar emetic, sold in ampoules containing a 1 per cent solution for intravenous injection. A course of tartar emetic treatment takes 20 days; the total dosage of the preparation per course is approximately

24 mg/kg, but not in excess of an absolute total dosage of 1.3 g for adults. After ten injections the dosage is decreased to avoid severe side effects, and it is again increased beginning with the 15th injection. For instance, a 60-kg patient is given 5 ml of 1 per cent tartar emetic in the first injection, 7 ml in the following injections up to the eleventh inclusively; the 12th through 15th injections contain 5 ml, and the 16th through 20th 7 ml per injection. Thus the patient receives a total of 130 ml of a 1 per cent solution of the preparation, or 1.3 g of tartar emetic. Injections are given every day. The efficiency of this treatment is about 60 per cent.

Of recent years the method of intensive tartar emetic treatment has been widely approved in China. The course of treatment is 2-3 days; the total dosage per course is 12 mg/kg, but no more than an absolute dose of 0.7 g. The method has been described above.

### PROPHYLAXIS

The drive against schistosomiasis is associated with numerous difficulties. Mass treatment of patients is an important factor. However, practice has shown that even wide-scale therapeutic measures do not ensure stable success. Thus Meleney (1954) reports that after a wide-scale treatment of schistosomiasis patients in Egypt the only result was a significant decrease in severe forms of the disease, while infestation of the population remained at its former high level. Meleney explains this by the fact that many patients do not complete the entire course of treatment owing to its protraction and the appearance of side effects.

Consequently, a planned campaign for dehelminthisation of the population must be incorporated with a combination of prophylactic measures—sanitary improvements in populated communities, disinfection of excreta, eradication of unnecessary water bodies, soil levelling, construction of dikes as protection against swamping, proper construction and management of irrigation systems.

In the Chinese People's Republic dehelminthisation of the feces is done by mixing them with urine in a 1:5 ratio. In this mixture the schistosome ova perish in 3 days in the summer and within a week in the winter.

Effective agents for exterminating the snail hosts are blue vitriol (copper sulfate), Paris green, DDT, calcium arsenate, and other preparations. Application of dimethyl and dibutyl phthalate ointments to the skin and special clothing and footwear prevent the penetration into the body of the schistosome cercariae.

### SCHISTOSOME DERMATITIS

Synonyms: bather's itch, swimmer's itch, swamp itch, water itch, cercarial dermatitis.

Schistosome dermatitis is a skin condition caused by the cercariae (larvae) of schistosomes.

## Historical data

In 1928, Cort first proved that the dermatitis observed in certain countries following bathing was caused by the penetration of the epidermis by cercariae of schistosomes.

## Etiology

The usual causes of this dermatitis are the cercariae of schistosomes parasitising in their mature stages in water fowl (ducks, gulls, swans); less frequently the disease is caused by cercariae of flukes parasitising in mammals (rodents and other animals). Dermatitis is also caused by the cercariae of the schistosomes of man: *S. haematobium*, *S. mansoni*, *S. japonicum* (see above).

Currently over 20 species of schistosomes are known to be able to penetrate under the human skin in their cercarial form. The overwhelming majority of species soon perish in the skin. Schistosome dermatitis is usually caused by the cercariae of *Trichobilharzia ocellata* and *T. stagnicola*.

*T. ocellata* (La Valett, 1854; Brumpt, 1931): in its stage of sexual maturity this fluke parasitises the blood vessels of domestic and wild ducks (teals). The intermediate hosts are fresh-water snails—*Limnaea stagnalis* *apressa* and *L. limosa*.

From the trichobilharzia ova voided with bird feces into water emerges a ciliate larva, the miracidium, that penetrates into a snail. In the body of the latter the larval forms of the fluke develop, and this development terminates in the formation of caudate cercariae. The cercarial body measures 0.25-0.41 mm in length by 0.05-0.1 mm in breadth, its tail is 0.35-0.45 mm long. The cercariae penetrate into the body of the ducks through the skin; in two weeks they attain maturity. These cercariae may penetrate into the skin of man and mammals, but they soon perish.

*Trichobilharzia stagnicola* (Tallo, 1936; McMullen and Beaver, 1945). The mature form has not been discovered in natural conditions. Experimental infestation was successful only with canaries. The intermediate host is the *Stagnicola emarginata angulata* mollusc.

## Epidemiology

Infection occurs when people bathe or wade in stagnant or slowly flowing fresh waters abundant with snails, the intermediate hosts of the schistosomes, and contaminated with the feces of birds, animals and humans, definite hosts of the fluke. The infection is transmitted to the snails by the definite hosts; the cercariae that emerge from the infested snails penetrate into the skin of man and cause schistosome dermatitis (swimmer's itch).

The infection may probably also be contracted while bathing in the sea.

Schistosome dermatitis is observed more commonly in the autumn during the migration of birds.

### **Geographical distribution**

Schistosome dermatitis has been described in the U.S.A., Canada, Germany, France, Africa, New Zealand, Australia, on the Hawaiian Islands; it has been registered in the U.S.S.R. (R. S. Chebotaryov et al., 1937). The disease is probably encountered in all countries, but is diagnosed as something else.

### **Clinical aspects**

The clinical features of schistosome dermatitis are highly variegated, differing with the individual. This is due to individual reactivity and the number of times infestation has occurred. The clinical features of a primary infection are usually manifested by an itch that appears 10-15 minutes after the penetration of the skin by the cercariae, and by macular eruptions. The latter appear an hour after immersion into the contaminated water and disappear in 6 to 10 hours. A second exposure causes a more acute form of dermatitis as a result of previous sensitisation; this dermatitis is accompanied by a very severe intermittent itch and the formation of erythematous patches and red papules.

McFarlane (1949) differentiates three types of papules.

1. Early primary papules appearing on the 2nd day. These papules are pale, do not itch, on the seventh day they become erythematous and slightly pruritic. Such papules are rarely observed.

2. Late primary papules, appearing on the 5th to 12th day following initial infestation; they persist for approximately two weeks, and are associated with a slight edema of the skin and an itch at the beginning.

3. Secondary papules, observed only in previously sensitised individuals (following repeated exposures). These papules are accompanied by edema, erythema, intense itching and blistering.

The total duration of schistosome dermatitis is 1-2 weeks; in severe cases it is longer.

### **Pathology and pathogenesis**

Upon contacting the skin the cercariae attach themselves to it and then burrow in. The propulsion of these parasites is facilitated by the existence on the anterior ends of their bodies of peculiar stylet-like growths and by outlets of special penetration glands that secrete a tissue-dissolving lysin. A swelling appears around the cercariae in the epidermis and the epithelial cells dissolve; as the flukes penetrate into the corium infiltrates appear in this tissue; the infiltrates are formed of polymorphonuclear leukocytes and lymphocytes; after several days the cercariae of bird and animal schis-

tosomes, incapable of development in the human body, perish as a result of a cellular reaction and the action of immune bodies. Of paramount importance in the pathogenesis of schistosome dermatitis are toxicoallergic reactions caused by sensitisation of the organism by the metabolic products of the helminths and by their waste, by the mechanical effect of the parasites and the tissue-lytic secretions of the penetration glands.

### **Treatment**

No specific treatment exists to date. The itch is alleviated by the application of ointments containing 5 per cent dimedrol (benadryl hydrochloride) in doses of 0.05 g 2-3 times a day.

Rp. Dimedroli 0.05  
Sacchari 0.3  
M.f. pulv.  
D.t.d. No. 10  
S. 1 powder 2 times a day

### **Prophylaxis**

The only possible prophylaxis is the extermination of the snail hosts of schistosomes. Particular attention must be paid to swimming pools. For individual protection it is recommended to rub the skin after coming out of the water. Lanolin ointments containing 40 per cent dimethyl phthalate or dibutyl phthalate are applied to the entire body before entering the water.



# CLONORCHIASIS

---

Clonorchiasis is a helminthic disease; its most salient features are involvement of the hepatobiliary system and the pancreas.

## HISTORICAL DATA

The causative agent of clonorchiasis in man was first discovered by McConnel in 1874, and described by Cobbold in 1875. The biology of this liver fluke was studied by Kobajashi (1910), Muto (1917) and Faust (1927).

## ETIOLOGY

The liver fluke (flatworm or trematode) *Clonorchis sinensis* (Cobbold, 1875) is responsible for the condition of clonorchiasis. Its flat body, tapering anteriorly and rounded posteriorly, measures 10 to 20 by 2 to 4 mm. An 0.45-0.6 mm in diameter oral suckorial disc or sucker is situated at the anterior end of the parasite; a ventral sucker, 0.4-0.47 mm in diameter, lies on the line dividing the first and second quarters of the body. The alimentary system consists of a mouth in the depth of the oral sucker, a pharynx and esophagus and two blind intestinal tubes lying tandem in the posterior third of the fluke. Two branching testes superimpose the intestinal ceca. Anterior to the testes there are an ovary and semen receptacle (spermatheca). Posterior to the ovary lies an ova-packed uterus opening in a genital pore anterior to the ventral sucker. In the median third of the body, lateral to the intestinal tubes, lie the vitelline glands. The operculated eggs are yellow-brown, the end opposite to the operculum is covered by a thick shell or cuticle. The eggs are 0.026 to 0.035 by 0.017 to 0.0195 mm (Fig. 87).

The definite hosts of the liver fluke in its stage of sexual maturity are man and carnivorous mammals. Rodents have been infected experimentally. In the bodies of their definite hosts the flukes concentrate in the intra- and extra-hepatic biliary ducts, the gall-bladder, and the pancreas. The

life-span of these parasites in man's body may be as long as 25 years, possibly even longer.

The eggs of the liver fluke are passed with the feces of the definite host; in water they are ingested by the intermediate host, *Bithynia fuchsiana*, *B. longicornis*, and other molluscs. The larval stages of the parasite develop and multiply in the body of the snail, where in approximately two months

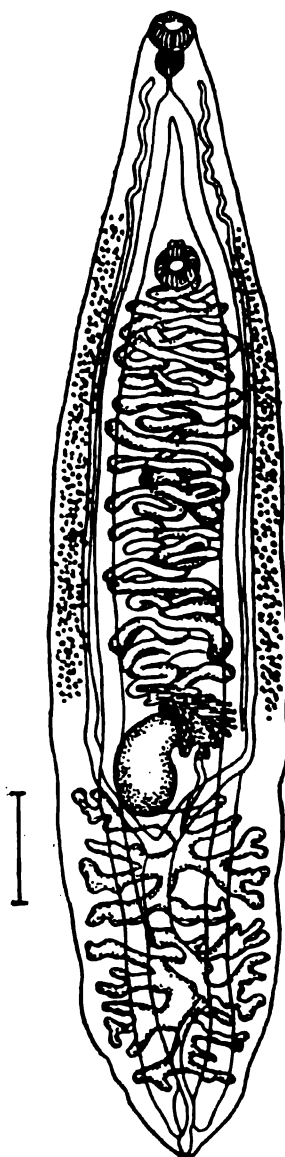


Fig. 87. *Clonorchis sinensis*  
(Cobbold, 1875) (K. I.  
Skryabin a. R. S. Schultz,  
1926)

the caudate cercariae are formed. The cercariae emerge into the water and penetrate the skin of fish (secondary intermediaries) into the subcutaneous fat and muscle tissue. Here they lose their tails and encyst as metacercariae. The secondary intermediate hosts of the liver flukes are various species of fish, chiefly of the carp family.

### EPIDEMIOLOGY

The principal conceptions of the epidemiology of clonorchiasis are based on knowledge of the biology of its pathogen. The feces of infested humans and animals are the source of infestation of snails, the snails transmit the parasites to fish; man and mammals become infested by ingesting raw and badly cooked fish containing the metacercariae of the

flukes. There is no other way. This type of helminthiasis is encountered chiefly in areas where the water is considerably contaminated with fecal matter, where there are great numbers of snails, the first intermediate hosts, and fish, the secondary intermediaries of the *Clonorchis*, and where the population uses raw and semi-raw fish for food.

### GEOGRAPHICAL DISTRIBUTION

Clonorchiasis is considerably widespread in China, Korea, and Japan; in the USSR it is observed among the inhabitants of the Amur river basin.

The largest site of the disease in the Chinese People's Republic is the Kwang Tung province, in some points of which up to 80 per cent of the population is infested.

In Southern Korea the infestation of the inhabitants of some villages of the Naktongan basin is also 80 per cent, in Fusan and adjacent areas it is 53-76 per cent.

In Japan the principal site of clonorchiasis is in the Okayama province where up to 50-70 per cent of the population is infested.

### CLINICAL ASPECTS

Clonorchiasis patients complain of pains in the right subcostal and epigastric regions, usually unconnected with intake of food. The type and character of these pains are highly variegated in different patients, and even in one and the same patient at various stages of the disease—from mild sensations of pressure to acute distress. Occasionally the pains assume a paroxysmal character resembling gall-stone colic. The pains irradiate to the spine, the right side of the neck, and in some patients to the left subcostal region. Other frequent symptoms are nausea, vomiting, dizziness, headache, increased nervous reactions, rapid mental and physical exhaustion.

Medical examination of the patient reveals pallor of the skin and mucous membranes, often a subicteric condition of the palate. Nutrition is usually normal or slightly lowered. The temperature is frequently subfebrile, higher levels are less common. The liver is mostly enlarged, firm, tender. Occasionally the distended gall-bladder may be palpated. In quite a few cases liver tests establish dysfunction of this organ, usually moderately expressed. Great numbers of the parasites and protracted duration of the disease sometimes lead to the formation of cirrhosis of the liver with clinical symptoms analogous to portal cirrhosis or Hanot's cirrhosis (cholangiolitic cirrhosis). The pancreas is, as a rule, very painful to palpation.

Microscopy of the duodenal juice reveals the eggs of the parasite, an increased mucus content, epithelial cells, occasionally leukocytes. B bile (the gall-bladder reflex) is in many cases obtained only upon repeated duodenal sounding. The gastric juice usually shows decreased acidity.

The differential blood count frequently shows eosinophilia (sometimes of a very high degree) and moderate macrocytic anemia.

Otto (1937) observed symptoms of periduodenitis and dyskinesia of the duodenum during X-ray examinations of clonorchiasis patients.

An analysis of the clinical features of clonorchiasis has shown that the most frequent lesions are cholangitis and dyskinesia of the biliary ducts; chronic hepatitis and pancreatitis are not rare; in some patients zooparasitic cirrhosis of the liver develops.

The clinical course of the disease is of a chronic nature, with periodic exacerbations. Occasionally a subclinical form of infestation is observed. Koenigstein (1949) described the first phase of the clinical course of clonorchiasis after the ingestion of infested fish by persons who had arrived from Europe into an endemic site of this disease. The result was infection of 20-30 per cent of the arrivals. The disease manifested itself as an acute infection. Several days after partaking of the infested fish malaise and pyrexia appeared (in some patients the fever went up to 40°). In the majority of patients a subicteric condition of the sclera and enlargement of the liver were observed; in a few cases splenomegaly was likewise noted. In 88 per cent of these patients the blood showed eosinophilia with a relative eosinophil count of 10-40 and even 80 per cent. In several weeks the acute symptoms of the disease cleared up and the eosinophil count went down. The clonorchis ova appeared in the feces 3-4 weeks after the onset of the disease. Koenigstein points out that such an acute course of the disease was observed only in newcomers; in the local population a relative immunity develops owing to infestation of several preceding generations. However, this opinion calls for corroboration.

## DIAGNOSIS

Diagnosis is established by laboratory examinations of the feces and duodenal juice of patients for demonstration of the parasite's ova. It must be pointed out that in endemic sites of this type of human helminthiasis infestation with another trematode — *Metagonimus yokogawai* — is not rare; the ova of this fluke are very much like the ova of the *Clonorchis* flukes. The latter are characterised by a pear-shaped form, a rough, coarse cuticle, marked projections of the shell in front of the operculum, a high operculum and a poorly discernible knob (B. A. Astafyev, 1960). The metagonimus parasitises the small intestine of man; it is easily eliminated by the administration of male fern extract or thymol. Dehelminthisation with subsequent examination of the stool for the parasites is in doubtful cases a valuable diagnostic measure. When it has been established that the patient harbours *Clonorchis sinensis* he should be subjected to thorough clinical, laboratory, and X-ray examinations in order to make a true clinical diagnosis, i. e., to find out whether angiocholitis (cholangitis), biliary duct dyskinesia, hepatitis, pancreatitis, cirrhosis of the liver and associated conditions are present. Only such a diagnosis makes it possible to employ proper therapeutic tactics in every individual case.

## PATHOLOGY AND PATHOGENESIS

The penetration of the liver flukes into the hepatobiliary system results in an adenomatous proliferation of the epithelium of the biliary ducts and the thickening of their walls owing to the development of connective tissue; in the cystous dilations formed in the lumens of the ducts the parasites and their eggs concentrate together with sloughed-off epithelial cells, mucus, eosinophils and neutrophils. Connective tissue grows round the involved ducts (periangiocholitis); this connective tissue growth sometimes surrounds entire lobules of the liver and even penetrates into these lobules between the layers of liver cells. Thus the presence of large numbers of parasites gradually leads to the development of cholangitic zooparasitic cirrhosis. The gall-bladder may be significantly enlarged.

The pancreas shows proliferation of the epithelium of the pancreatic ducts, thickening of their walls and dilatation of the lumens; sclerotic changes are observed around the ducts.

The principal part in the pathogenesis of clonorchiasis is played by toxico-allergic reactions, the mechanical action of the flukes, neuroreflexory influences, the development of conditions conducive to the appearance of secondary infections of the biliary ducts and premises for the development of primary cancer of the liver.

The toxico-allergic reactions are the result of the action of the metabolic products eliminated by the parasites. The organism is sensitised by these products, resulting in an allergic reconstruction, one of the signs of which is the eosinophilia so often observed in clonorchiasis.

The mechanical action of the liver flukes consists of the damage they inflict on the walls of the biliary and pancreatic ducts and the gall-bladder with their suckorial organs and spines that cover the surface of the young forms. Accumulations of the parasites impede the outflow of the bile and of the pancreatic secretion. Cases have been described in which the common bile duct was completely blocked by the parasites and retention jaundice developed owing to this. Otto and Tschan-Tsching (1935) have described complete obstruction of the cystic duct by the *Clonorchis* ova. The influence of nerve reflexes is conditioned by the mechanical, and possibly also toxic stimulation of the nerve elements in the ducts, as a result of which pathological nerve impulses are formed; these impulses are conveyed first of all to the stomach and duodenum that are closely connected anatomically and physiologically with the hepatobiliary system and the pancreas. These impulses impair the secretory and motor functions of the stomach and the mobility of the duodenum.

Stimulation of the vagus and sympathetic nerves causes dyskinesia of the biliary ducts and gall-bladder. Dyskinesia of the biliary ducts, accumulation in these ducts of the parasites, their eggs, sloughed-off epithelial cells, mucus, and associated inhibition or even complete obstruction of the bile flow create conditions conducive to the development of bacillary infections, the pathogens of which penetrate into the liver by descending (with the blood) and ascending (from the intestine along the ducts) routes.

Glandular proliferation of the epithelium of the biliary and pancreatic ducts should be looked upon as a pre-cancer condition that in some cases develops into cancer. This is confirmed by the observations of Katsurada (1897), Porter and Pipie (1922), and of other authors. Olt (1927) established the presence of cancer of the liver in 1.14 per cent of clonorchiasis patients, and in only 0.35 per cent of persons not afflicted with this type of helminthiasis.

## TREATMENT

*Specific treatment* for clonorchiasis has been studied insufficiently. Partial success is obtained with antimonous (trivalent antimony) preparations—tartar emetic, antimonium sodium tartrate and fuadin, prescribed as for schistosomiasis. Some authors prescribe gentian violet perorally, 0.08-0.1 g 3 times a day for 15-20 days. Nordone (1948) combined the injection of fuadin and ingestion of gentian violet with a surgical fistula of the gall-bladder; through this fistula dead and living flukes were discharged; after 20 days the cannula was removed from the gall-bladder; the surgical wound soon closed and the patient was transferred to out-patient treatment with gentian violet. Complete recovery was attained in all 12 patients treated in this manner. However, it is absolutely clear that the method proposed by Nordone is too complicated for extensive introduction.

In recent years reports have been published on the successful treatment of clonorchiasis with chloroquine. As the method is still in the stage of evolution we shall only cite the results of observations of several individual authors.

Basnuevo (1949) prescribed chloroquine phosphate, giving 1 g per day for 3 days and then 0.5 g per day for 20 days, a total dosage of 13 g for the entire course; he reported the recovery of 2 out of 5 patients.

Chung Huei-lan et al. (1954-55) treated 8 clonorchiasis patients with chloroquine; in six of them recovery was secured by the administration of average daily doses of 10.4 mg/kg of the preparation; the total dosage per course averages 405 mg/kg (absolute dose 19.5-30 g), the duration of treatment was 20 to 53 days. Positive results in the treatment of clonorchiasis with chloroquine were also obtained by Crane (1955) and his staff. Negative results were reported by Edelman and Spingarn (1949).

The present authors hold that hexachloroethane is a preparation that certainly deserves to be tested, as they have found it to be effective in the treatment of another helminthiasis of the hepatopancreatic system—opisthorchiasis (Vinogradov's disease), a condition closely related to clonorchiasis. With hexachloroethane considerable subsidence and even disappearance of clinical symptoms was effected in the majority of opisthorchiasis cases, and the infection lost its virulence; in part of these patients complete clinical recovery and elimination of the infection was attained. L. I. Sinovich (1956) in experiments on cats demonstrated the helminthocidal properties of hexachloroethane in clonorchiasis.

Hexachloroethane is prescribed for peroral administration on 2 successive days; the daily adult dose is 6-8 g, the total dose for one course is 12-16 g.

The patient is given the preparation one hour after a light breakfast, 2 g every 15 minutes. If necessary, the course is repeated 2-3 months later.

Rp. Hexachloroethani 1.0  
D.t.d. No. 12 in caps.  
S. 2 capsules 3 times a day

For children the daily hexachloroethane dosage is 0.1 g/kg. The side effects evoked by this preparation are negligible, expressed in some instances by an intoxication similar to drunkenness, by headache, dizziness, occasional intensification of abdominal pains; diarrhea is rare. All these symptoms disappear the day following the ingestion of the medicine.

In the treatment of clonorchiasis patients both specific and symptomatic therapy is necessary; the latter is efficacious even when it is impossible to prescribe helminthocidal preparations. Non-surgical bile drainage by means of the duodenal tube has been found beneficial for angiocholitis and dyskinesia of the biliary ducts; bile secretion is stimulated with magnesium sulfate. The procedure is carried out once or twice a week for one or two months. Another method of non-surgical bile drainage is the one recommended by Demyanov; this author advises patients to take tepid 33 per cent magnesium sulfate (15-30 ml) on an empty stomach (once or twice a week) and then to lie for 2 hours on the right side. The prescription of cholagogues is likewise expedient (e. g., cholosas, an extract of dogrose hips, 1 teaspoonful 3 times a day half an hour before meals), antispastic agents (papaverine, belladonna, etc.), diathermy or hot water bags (or heating pads) to the liver area. Substances prescribed for dysfunctions of the liver, and particularly for cirrhosis, are glucose, ascorbic acid, liver preparations (campolon or antianemin) or vitamin B<sub>12</sub>, 200-400 g of curds (cottage cheese) daily or methionine in 1 g doses 3 times a day for one or two months, with intervals. A good preparation for preventing and even eliminating fatty infiltration of the liver cells is lipocain (lipocaic), a substance obtained from the pancreas of slaughtered cattle; this preparation is given per os, 0.1-0.2 g 3 times a day for 10-12 days. Secondary infections of the biliary tract are treated with antibiotics—penicillin, streptomycin, or biomycin (aureomycin). It is highly desirable to select the preparation by establishing the reactivity of the duodenal flora to it (in specimens of duodenal juice).

### PROPHYLAXIS

Individual prophylaxis is realised by eating only thoroughly cooked fish. Sanitary enlightenment is an important factor in gaining control of clonorchiasis, as are the protection of waters against contamination with fecal matter, and sanitary control in public catering enterprises and fisheries in order to prevent the sale of infestive fish.

# OPISTHORCHIASIS VIVERRINI

---

*Opisthorchiasis viverrini* is a worm disease in which the principal sites of lesion are the liver, gall-bladder, and pancreas.

## ETIOLOGY

The causative agent of this disease is the fluke (trematode) *Opisthorchis viverrini* (Poirier, 1886; Stiles a. Hassal, 1896). The flukes recovered from the human body measure 5.4 to 10.2 mm in length and 0.8 to 1.9 mm in breadth. The diameters of their suckers are 0.23 mm. The oral sucker is terminal, the ventral sucker is on the line between the anterior and middle part of the body. The mouth is in the depth of the oral sucker; it leads into a pharynx and esophagus; two intestinal tubes fork off from the esophagus at acute angles, and end blindly in the posterior part of the body. The esophagus is three times as long as the pharynx. Two four-lobed testes lie in the posterior part of the fluke, and a multi-lobed ovary — anterior to them. Lateral to the ova there is a semen receptacle. The vitelline glands are visible as clumps (follicles) lateral to the intestinal ceca in the middle part of the body. Anterior to the ovary, between the intestinal tubes, there is an ova-filled uterus with an outlet anterior to the ventral sucker and adjacent to the male opening. The eggs are yellow-brown, operculated, with cuticular thickenings at the poles; they measure 0.019-0.029 by 0.012-0.017 mm. The mature *Opisthor-*

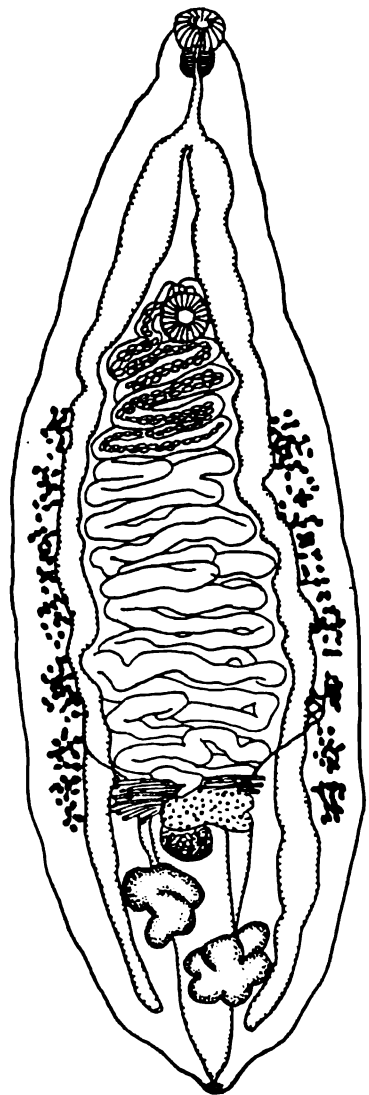


Fig. 88. *Opisthorchis viverrini* (Poirier, 1886) (Furman, 1928)



*chis viverrini* parasitise the hepatic biliary ducts, the gall-bladder, and the pancreatic ducts of man, domestic cats, civet-cats (carnivores of the genus *Viverra*), and dogs (Fig. 88). The intermediate hosts to this liver fluke are snails, most probably of the genus *Bithynia*. The secondary intermediaries are fresh-water fish.

### EPIDEMIOLOGY

The epidemiological aspect of opisthorchiasis *viverrini* is close to that of clonorchiasis. The eggs of the opisthorchis flukes are passed with the feces of infested people and animals, and are subsequently ingested by snails. The cercariae of the flukes emerge from the snails and then penetrate into fish. Man and animals are infested by consuming raw or partly cooked fish.

### GEOGRAPHICAL DISTRIBUTION

The principal site of opisthorchiasis *viverrini* is Thailand; in the north-eastern provinces of this country 2.6 to 55.5 per cent of the population are infested. The disease has likewise been registered in India and on Taiwan.

### CLINICAL ASPECTS

The clinical features of opisthorchiasis *viverrini* have been studied sparsely. Basically they coincide with the features typical of clonorchiasis. Sadun (1955) states that the early symptoms of the disease are debility, pain in the liver area, occasionally jaundice, diarrhea, nettle-rash, eosinophilia in the blood. Cirrhosis of the liver and primary cancer of this organ are encountered more frequently in opisthorchiasis *viverrini* foci than in other places. Cirrhosis of the liver affects both adults and children. Sadun found 5,896 opisthorchis flukes in the liver of a child that had succumbed to the disease.

### PROPHYLAXIS

Prophylactic measures against opisthorchiasis *viverrini* are the same as for clonorchiasis.

### TREATMENT

The therapy of the disease has still to be developed. Sadun and Chammarkitch (1953) tested the effects of chloroquine phosphate (aralen diphosphate), administering it by mouth for 3 days in daily doses of 1 g, and then giving 0.5 g daily for 20 days; the total dose given each patient was 13 g of the preparation. Twelve patients were examined 40-50 days subsequent to treatment. The number of ova had by then decreased in seven patients and increased in two. Thus the results obtained do offer some hope. The present authors consider that hexachlorethane should also be tried.

## AMPHYMEROSIS (OPISTHORCHIASIS NOVERCA)

---

*Amphymerosis* or *opisthorchiasis noverca* is a worm disease of the liver caused by the liver fluke *Amphymerus noverca* (syn. *Opisthorchis noverca*) (Braun, 1902). This fluke was first discovered in man in India in 1876-78, by McConnell.

The *Amphymerus noverca* fluke is either lanceolate or ovoid in shape; it is 9.5 to 12.7 mm long and 2.5 mm broad. The surface of its body is studded with minute spines. The two suckers are situated nearer to each other than in the other liver flukes, the oral sucker is larger than the ventral sucker. The oral sucker is directly followed by a round pharynx; no esophagus is present. The testes lie obliquely in the posterior part of the body, the ovary in front of them. The terminal part of the vitellaria are adjacent to the posterior testes. The uterus is situated between the ovary and the ventral sucker. The elongated ova measure 0.034 by 0.019 mm. The fluke inhabits the biliary ducts of man, dogs, foxes, and pigs. The life cycle of this fluke, its pathogenesis, and the clinical features of the condition caused by it have not been studied. Infection is probably acquired through fish.

# METAGONIMOSIS

---

Metagonimosis is a worm disease characterised by intestinal disorders.

## HISTORICAL DATA

In man the disease was first described by Yokogawa in 1911; this author proved that the infection is contracted by man and carnivores through fish.

## ETIOLOGY

The pathogen of metagonimosis is the fluke *Metagonimus yokogawai* (Katsurada, 1913). Its body measures 1 to 2.5 mm in length and 0.4 to 0.7 mm in breadth; the cuticle is covered with tiny spines. The ventral sucker is combined with the genital pore. The mouth leads into a prepharynx followed by a pharynx, a long esophagus and two intestinal tubes. The rounded testes are posterior. The ovary and receptaculum seminis are situated in front of the testes. The uterus is between the ventral sucker (and genital pore) and the posterior testis. The vitellaria (yolk glands) are 10-12 large follicles in the posterior quarter of the body, over the intestinal tubes (Fig. 89). The operculated eggs measure 0.026 to 0.032 by 0.015 to 0.017 mm. Their cuticles are thickened at the pole opposite the operculum. The definite hosts of the metagonimus are man, dogs, cats; the fluke lives in the small intestine. The first intermediaries are fresh-water snails—*Melania libertina*, *Blanfordia nosophora*, *Piradus cingulatus* and others. Various species of fish serve as secondary intermediaries.

In the Amur basin the larvae (metacercariae) of the metagonimus have been discovered in the whitefish (*Coregonus ussuriensis*) and carp (*Cyprinus carpio*), the Amur ide (*Leuciscus valeckii*) and Amur bream (*Parabramis pekinensis*), and in various other fish, including *Pseudaspius leptcephalus*, *Hemibarbus labeo*, *Gobio gobio*, *Carassius auratus gibelio*, *Culter erythropterus*, *Xenocypris macrolepsis*, *Hypophthalmichthys molitrix*, *Parasilurus*

*asotus*, *Pseudobagrus fulvidraco*, *Liocassis ussurensis* and *Liocassis brashnikowi* (G. A. Zmeyev, 1932, 1947). In Japan the secondary intermediaries of the metagonimus are *Carassius auratus*, *Leuciscus paluensis* and *Pleoglossus altivelis*.



Fig. 89. *Metagonimus yokogawai* (Katsurada, 1912)  
(K. I. Skryabin, V. P. Podypolskaya a. R. S. Schultz, 1930)

According to Zmeyev the metacercariae of the flukes localise in the scales, fins, and gills of the fish; Japanese authors hold that they also penetrate into the subcutaneous fat and muscles. The metacercariae are spheroid 0.18-0.20-mm cysts, encapsulating the mobile larvae.

### EPIDEMIOLOGY

The source of metagonimosis are infested humans, dogs, and cats. The ova of the parasite are voided with the feces. In water the larvae hatch from the ova and actively burrow into the bodies of snails. In the latter the parasite goes through several larval stages of development and multiplication, terminating in the formation of cercariae. The cercariae emerge into the water, penetrate into fish and there become encysted, turning into

metacercariae. Man contracts the infection by consuming raw fish, or upon accidental ingestion of infested fish scales that may have become attached to a dish or cooking utensil or bread and thus conveyed into the liquid of an already cooked dish. In some areas the chief source of transmission of the infection is a national dish, "tala", the basic part of which is raw fish finely minced together with the scales.

Fish infestation occurs for the most part in river and lake backwaters contaminated with fecal matter and abundant in snails.

### **GEOGRAPHICAL DISTRIBUTION**

Metagonimosis is quite widespread among the population of Korea, Japan, China, the Philippines. In the U.S.S.R. a site of this helminthic disease exists in the Amur basin.

### **CLINICAL ASPECTS**

Some cases of metagonimosis may be of a subclinical type, but frequent symptoms are nausea, salivation, abdominal pains, and occasionally a very persistent relapsing diarrhea with viscid or liquid stools voided 5-6 times a day.

### **DIAGNOSIS**

Diagnosis of metagonimosis is a difficult matter as the ova of its pathogen are very much like the ova of clonorchis flukes. Moreover, frequently one and the same patient may be simultaneously afflicted with both clonorchiasis and metagonimosis. The characteristic features of the ova of *Metagonimus* are a lemon-shaped, smooth, thin cuticle, the absence of any projection in front of the flat operculum, and a well-defined knob. In doubtful cases it is necessary to resort to test dehelminthisation with subsequent examination of the feces.

### **PROGNOSIS**

Prognosis is favourable. If repeated infestation is excluded spontaneous elimination of the flukes is possible as they gradually pass into the lower sections of the intestine and are voided with the feces.

### **PATHOLOGY AND PATHOGENESIS**

These aspects of metagonimosis have been studied very little. When the metacercariae of the metagonimus penetrate into the intestine the larvae emerge from their cysts and work their way into the mucous membrane, burrowing narrow tracks; in two weeks sexual maturity is attained and the parasites emerge into the intestinal lumen. As a result of the mechanical, and possibly also the toxic, action of the flukes catarrhal enteritis develops in the intestine.

## **TREATMENT**

Dehelminthisation is effectedd with thymol, tetrachloroethylene, male fern extract. Thymol is prescribed for two successive days, 2 g twice a day over a two-hour interval; two hours after the second dosage a saline cathartic is administered. Tetrachloroethylene is given as for ankylostomiasis. L. I. Sinovich holds that the most effective preparation is fern extract; he prescribes 6-7-g doses on an empty stomach for adults. On the day preceding treatment and 1½-2 hours following it the patient is given a saline cathartic. The present authors are of the opinion that lower dosages of fern extract should be tried (2.0-2.5 g). Subsequent examination of the feces may reveal the eggs of the parasites owing to the low effect of anti-helminthic preparations on the parasites in the intestinal walls; in such an event treatment must be repeated.

## **PROPHYLAXIS**

Preventive measures are the same as for clonorchiasis.

# HETEROPHYIASIS

---

Heterophyiasis is a helminthic disease clinically characterised by intestinal disorders; however, migration of the ova into various organs and tissues occasionally causes corresponding lesions (of the brain, for instance).

## ETIOLOGY

The causative agent is the minute intestinal fluke *Heterophyes heterophyes* (Siebold, 1852). The cuticle of the pyriform body is thickly studded

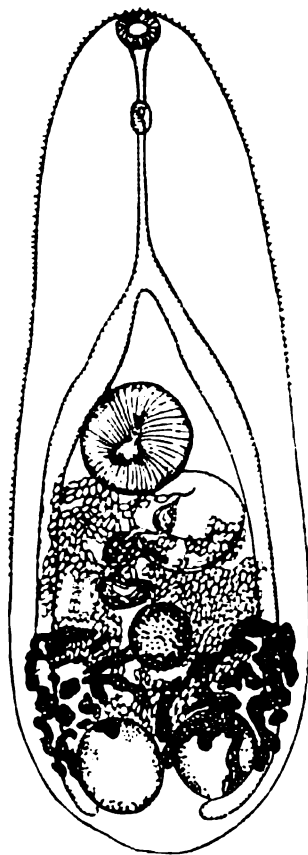


Fig. 90. *Heterophyes heterophyes* (Witenberg, 1929)

with spines; the body measures 1-2 mm in length and 0.4-0.5 mm in breadth. Besides the oral and ventral suckers there is a third one, the so-called genital sucker, in the depths of which the genital pores are situated.

The alimentary system is represented by a pre-pharynx, pharynx, esophagus and two intestinal ceca. The ovoid testes are posterior, the globular ovary and the receptaculum seminis are in front of the testes, the uterus is between the ventral sucker and the ovary. The vitelline glands, situated posteriorly over the intestinal tubes, consist of two clumps, each of which is made up of 14 follicles (Fig. 90). The operculated ova are encased in a thick cuticle; they measure 0.028-0.030 by 0.015-0.017 mm. The flukes inhabit the small intestine of their definite hosts—man, dogs, cats, foxes. The first intermediaries are fresh-water snails *Pironella conica*, *Melania tuberculata*, *Cleopatra bulinoides*, and some others. The secondary intermediaries are several species of fish, among them the mullet (*Mugil cephalus*) and the minnow (*Gambusia affinis*). Besides *H. heterophyes* certain other closely related species of flukes have been reported to cause heterophyiasis: *H. breviceca*, *H. taihokui*, *H. katurada*.

### EPIDEMIOLOGY

When the heterophyes ova are voided with the feces of the definite hosts they already contain fully developed larvae—miracidia. The miracidia hatch only after ingestion by the appropriate snail. In the body of the snail the parasite goes through several larval stages—sporocysts, one or two generations of rediae, and, finally, the cercariae. The latter emerge into the water where they penetrate into fish and encyst in their subcutaneous tissue and muscles. Man becomes infested by consuming raw or partly cooked fish.

### GEOGRAPHICAL DISTRIBUTION

Heterophyiasis is common to Egypt and countries of the Far East. It has been registered in Greece.

### CLINICAL ASPECTS

The condition is accompanied by loss of appetite, pain in the upper part of the abdomen, diarrhea alternating with constipation; mucus is occasionally observed in the stool. Migration of the ova to the brain may cause epileptoid paroxysms and even fatal hemorrhages. Involvement of the muscles and valves of the heart may lead to cardiac failure.

### DIAGNOSIS

Diagnosis is based on the demonstration of the eggs of the flukes in the stool. It must be remembered that these ova are very much like the ova of the clonorchis and metagonimus flukes, therefore in doubtful cases test dehelminthisation is resorted to.



## **PROGNOSIS**

In the event of lodgement of the ova in the heart or brain prognosis may be very grave.

## **PATHOLOGY AND PATHOGENESIS**

By inhabiting the small intestine the heterophyes flukes cause catarrhal inflammation of the mucous membrane, occasionally its superficial necrosis. A case of brain hemorrhage caused by heterophyes ova has been reported (Africa et al., 1936). Gallais and co-workers (1955) observed a connective tissue capsule, 6 mm in diameter, formed around an accumulation of heterophyes eggs. The eggs were likewise lodged in the deep layers of the intestinal wall, the mesenteric lymph nodes, and the muscle and valves of the heart.

## **PROPHYLAXIS**

It is recommended to abstain from consuming raw or semi-raw fish. Public prophylaxis is realised by protecting water supplies against fecal contamination.

## **TREATMENT**

The drugs used are thymol, male fern extract, and chenopodium oil.

## NANOPHYETOSIS

---

The causative agent of this disease is *Nanophyetes schichobalowi* (Scryabin and Podyapolskaya, 1931). This is a very small trematode worm; its dimensions are only 0.5 by 0.47 mm, its shape is almost globular. Large testes are located in the posterior and widest part of the fluke. Numerous yolk glands are distributed all over its body in the form of small follicles or clumps. The ova have a strong resemblance to the ova of the fish tapeworm (*Dyphyllobothrium latum*); they measure 0.062-0.072 by 0.043-0.048 mm. This fluke was first discovered by K. I. Scryabin and V. P. Podyapolskaya in 1931 in Khabarovsk. The first intermediary is the snail *Semisulcospira laevigata*, the second intermediaries are fish of the *Thymalidae* and *Salmonidae* families (L. V. Filimonova, 1960).

The clinical features of this disease have not been studied. Dehelminthiasation is performed by the administration of male fern extract and thymol.

# PARAGONIMIASIS

---

Paragonimiasis is a helminthic disease with a prevalent site of lesion in the respiratory organs.

## HISTORICAL DATA

In 1880, Baelz and Manson described the clinical features of paragonimiasis and demonstrated the ova of the paragonimus lung fluke in the sputum of a patient. Ringer was the first to find the adult fluke (1881); this trematode was later described by Cobbold under the name of *Distomum ringeri*.

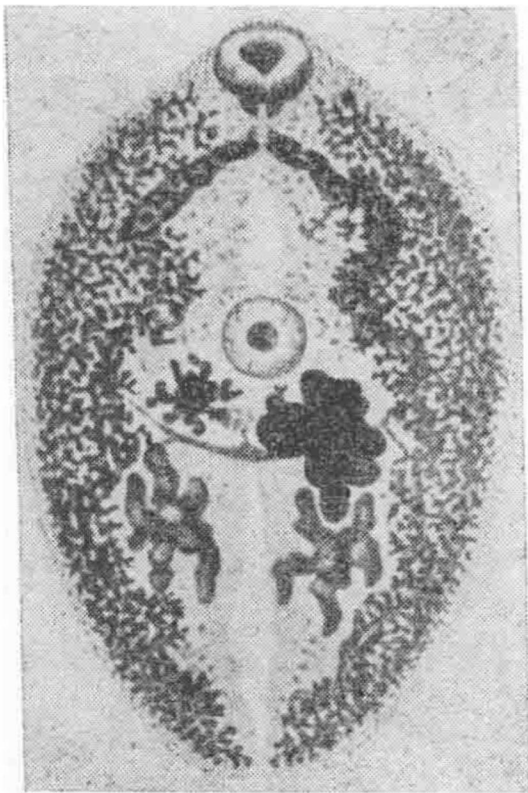


Fig. 91. *Paragonimus westermani*  
(Faust)

## ETIOLOGY

Paragonimiasis is a morbid condition caused by the lung fluke *Paragonimus westermani* (Cobbold, 1880), also known as *P. ringeri*. The living fluke is reddish-brown, its ovoid body measures 7.5-13 mm by 4-8 mm and is 3.5 to 5 mm thick. The cuticula is studded with wedge-shaped spines. The oral sucker is anterior, the ventral sucker lies in the centre of the body; the fluke possesses a pharynx and short esophagus: two meandering intestinal tubes terminate blindly in the posterior part of the body. The testes and ovary are lobulated. The common genital pore lies close to the posterior margin of the ventral sucker. Well-developed vitelline glands are situated

in the lateral parts of the body (Fig. 91). The operculated elongated ova are golden-brown, and measure 0.08-0.118 by 0.048-0.060 mm. The mature fluke infests man, dogs, cats, pigs, and the Ussuri tiger. Localisation is chiefly in the small bronchi, but the parasites are also found in the pleura, diaphragm, pancreas, intestine, the mesenteric lymph nodes, the prostate, liver, skin, brain, and other organs and tissues. The flukes exist in these organs in fibrous capsules 10 to 35 mm in diameter; each capsule usually contains two paragonimus flukes. The first intermediate hosts of the paragonimus are *Melania* and other snails. The secondary intermediaries are fresh-water crabs of the genera *Potamon*, *Eriocheir*, and others, and crawfish of the genus *Cambaroides*.

### EPIDEMIOLOGY

The paragonimus eggs are ejected with the sputum and feces of the definite hosts of this parasite. In water it takes 16 to 60 days for a ciliate larva—a miracidium—to develop in the egg; the miracidium emerges into the water and then penetrates into the first intermediary—a snail. In the snail the parasite goes through several successive larval generations of development and multiplication terminating in the emergence into the water of the cercarial stage. The cercariae penetrate into crabs and crawfish and become encysted in the muscles, liver, and other organs of these crustaceans, turning into metacercariae. It is also possible that the crabs become infested by devouring infested snails. Thus, infested people and animals transmit the infection to snails, from the latter it is passed on to crabs and crawfish. Man contracts the infection by consuming raw or poorly cooked crabs and crawfish, or by accidentally swallowing particles of their muscles or other organs while preparing food, and also probably by drinking water containing fragments of crabs and crawfish.

In some countries the metacercariae of the lung flukes penetrate into the human body with raw crab juice employed in national medical lore as a remedy for “chills and fevers”. In the intestine of the definite host (man, dogs, etc.) the paragonimus larvae free themselves of the membranes they are covered with and then penetrate through the intestinal wall into the peritoneal cavity from whence they work their way into the lungs, and occasionally also into the brain and other organs; in three months the parasite attains sexual maturity. The migration of the larvae with the blood stream is likewise not excluded.

### GEOGRAPHICAL DISTRIBUTION

Paragonimiasis is common to certain areas of Thailand, Korea, China, Japan, Indo-China, India, the Philippine Islands; it is encountered in Africa, Malaya, on the Solomon Islands, and in America.

In South Korea up to 6.1 per cent of the population of some localities is infested with the paragonimus fluke; in North Korea infestation is approximately 1.3 per cent of the population.

In China this helminthiasis is encountered in the provinces of Che Kiang, Hu Peh, Fu Kien, Yun Nan, and on Taiwan.

Up to 5-10 per cent of the population is infested with paragonimiasis in some villages of the Shizuoka prefecture in Japan.

In the U.S.S.R. only 3 cases of paragonimiasis of local origin have been discovered among the inhabitants of the Far East. In Soviet literature paragonimiasis has been described by K. I. Scryabin et al. (1927), and by other authors.

### CLINICAL ASPECTS

Onset is usually insidious. A slight morning cough with expectoration of a sparse volume of mucous sputum appears. The cough intensifies gradually, the quantity of sputum increases, blood clots and yellowish-brown lumps containing eggs of the parasite appear in it; pains develop in the chest, in some cases the temperature rises to subfebrile levels or even higher. On auscultation of the lungs dry or, less frequently, moist fine bubbling rales are elicited; occasionally pleural crepitations may be heard. The paragonimus ova and considerable numbers of erythrocytes and eosinophils are demonstrable in the sputum; secondary infection may cause the sputum to become purulent. The diurnal volume of sputum, even in the absence of bronchiectasis, may attain 500 ml. Eosinophilia associated with a normal or somewhat increased white blood count is not infrequent.

In some patients exudative pleurisy sets in. According to B. Zagrafski and G. Terziyev (1956) the characteristic feature of paragonimiasis pleurisy is a prolonged benign course accompanied by normal temperatures and ESR. The pleural fluid is cloudy and greyish-yellow; it almost always contains crystals of cholesterol, drops of lipids and the eggs of the parasite. In some instances a hemorrhagic pleurisy and, in the presence of secondary infection, even empyema may develop. Ch'iene Mu-han (1955) defined four stages of pulmonary paragonimiasis by the roentgenographic method.

1. *Stage of infiltration.* Its duration is one or two months following infestation; the clinical symptoms are feverish chills, coughing, and sputum devoid of blood clots or paragonimus ova. Irregularly contoured infiltration sites are visible on the roentgenogram.

2. *Stage of cyst formation.* This stage is accompanied by a low fever, a cough with expectoration of a rusty sputum containing the eggs of the paragonimus fluke, frequently hemoptysis is observed. X-ray examinations show the presence of moderately intensive nodular opacities measuring 8 to 37 mm in diameter; around these opacities radial linear shadows are visible, and in them 2-6-mm vacuoles.

3. *Stage of fibrosis.* The clinical symptoms of the disease disappear; X-ray findings are small isolated fibrotic sites producing intensive shadows, surrounded by short radial opacities.

4. *Stage of calcification.* This stage is asymptomatic. X-ray examination of the lungs reveals solitary or multiple sites of calcification producing a dense homogeneous shadow 2-5 mm in diameter.

Long-term affliction and multiple infestation lead to the development of pneumosclerosis and pulmonary heart.

Paragonimiasis of the central nervous system results in encephalitis, meningoencephalitis, or the syndrome of brain tumor. In the latter case symptoms pointing to increased intracranial pressure appear: headache, dizziness, vomiting of a central nervous origin, congested optic disks, impairment of vision, mental changes, general and focal epileptoid attacks, bradycardia; occasionally pareses, paralyses, and sensory disturbances appear. At late stages of the disease X-ray examinations of the cranium reveal rounded shadows of various dimensions—the calcified cysts of the paragonimus flukes. Encephalography or ventriculography demonstrate dilatation and deformation of the lateral ventricles of the brain (P. Petrov, 1956).

### DIAGNOSIS

The diagnosis of pulmonary paragonimiasis is based on clinical, roentgenologic, and laboratory findings (the latter constitute demonstration of the paragonimus ova in the feces and sputum of the patient). During the first three postinfection months, when the parasites have not yet attained sexual maturity, the eggs are not demonstrable. In this period a great diagnostic aid may be provided by immunological reactions—cutaneous and allergic tests and the complement-fixation test; these reactions, according to Chung Huei-lan (1956) become positive in two to three weeks after infestation.

The most valuable X-ray findings are obtained by doing a series of roentgenograms in different projections and also sectional roentgenography (tomography). In differential diagnosis tuberculosis, pulmonary tumour, and bronchiectasis must be accounted for. The absence of tuberculosis bacilli in the sputum, negative immunological tests for tuberculosis and the specific features of this disease permit it to be excluded without any particular trouble. Ch'iene Mu-han (1955) considers radiography to be very helpful in this respect, as it demonstrates the vacuoles in the cysts and the radial opacities surrounding them; no such picture is ever observed in tuberculosis. Pulmonary tumours produce denser opacities than paragonimiasis does; the opacity does not expand in paragonimiasis, while in the case of a tumour it does, and quite rapidly. Bronchiectasis is excluded on the basis of roentgenographic and bronchographic data.

### PATHOLOGY AND PATHOGENESIS

The penetration of the young paragonimus flukes into the lung tissue evokes infiltration of this tissue by eosinophils and neutrophils, lymphocytes, plasmacytes, and fibroblasts. After some time a fibrotic capsule is formed around the parasites; this capsule opens into a bronchial lumen. The pleural membranes are frequently thickened in paragonimiasis; exudative pleurisy occasionally develops. Involvement of the central nervous system by the migration of the parasites or their ova to the brain results in

cerebral tissue necrosis. B. P. Konstantinova (1956) described a case of polyserositis caused by the dissemination of the *paragonimus* ova throughout the peritoneum, pleura, pericardium and cerebral membranes.

Of paramount significance in the pathogenesis of paragonimiasis are toxico-allergic reactions and the mechanical effect of the flukes and their eggs on the tissues. The latter may at times be transferred metastatically to distant organs and tissues by the blood or lymph flows. In some instances the disease is complicated by a secondary infection.

### TREATMENT

Great difficulties are encountered in the treatment of paragonimiasis. Currently the most frequently employed agent is emetine. The treatment consists of 4 or 5 three-day cycles with four-day intervals between them. A 2 per cent solution of the preparation is injected subcutaneously or intramuscularly; the adult dosage is 1.5 ml (0.03 g of the preparation) twice a day. Chinese authors prefer to protract the cycle of treatment to 5-7 days; they administer two, sometimes more, cycles over intervals of seven days. Emetine therapy produces clinical improvement in almost all cases, but a stable disappearance of the ova is observed in no more than 30 per cent of patients.

During emetine therapy electrocardiograms must be performed regularly in order to be able to discontinue the treatment upon the appearance of myocardial involvement. In recent years hopeful results have been obtained in the treatment of paragonimiasis with chloroquine; Chung Huei-lan and his co-workers (1954) prescribed this preparation for adults in 0.5 g doses twice a day intermittently over a period of 93 to 231 days. The total dose for a course of treatment was 26.84 to 85.75 g.

Yokogawa et al. (1961) and other authors report good therapeutic effects in the treatment of paragonimiasis with bithionol (synonyms: actamer, bitin, 2,21 thiobis [4,6-dichloropheno]) which they administered on alternate days for a period of 5 to 15 days; the daily dose was 50 mg per kg of body weight.

In cases of cerebral paragonimiasis accompanied by increased intracranial pressure decompression is effected by surgical trephination, and sometimes the cysts of the parasite are removed from the brain by surgery (P. Petrov, 1956).

### PROPHYLAXIS

Prophylactic measures resolve into abstaining from eating raw or partly cooked crabs and crawfish, and keeping hands, clothing, and kitchen utensils scrupulously clean when preparing dishes containing crustaceans. Public prophylaxis is realised by the introduction of sanitary measures to protect water supplies against contamination with fecal matter.

# FASCIOLIASIS

---

Fascioliasis is a helminthic disease that prevalently affects the hepatobiliary system.

## HISTORICAL DATA

The first authentic case of fascioliasis in man was established by Pallas in 1760, although the discovery of fasciola flukes was earlier reported by Malpighi (1698). In 1922, Seifert conceived the idea of the expediency of treating fascioliasis with emetine. The truth of this assumption has been proved clinically by Soviet authors: A. P. Vasilyeva (1927), O. N. Pavlova (1927), G. M. Semyonov and D. A. Kogan (1927), and subsequently by authors of other lands.

## ETIOLOGY

Fascioliasis is caused by two species of trematodes of the genus *Fasciola* (L., 1758): *F. hepatica* (L., 1758) and *F. gigantica* (Cobbold, 1855).

*F. hepatica* is a spatulate fluke measuring 20-30 mm in length and 8-12 mm in breadth. The anterior part of the body is studded with minute spines and is drawn out into a proboscis which carries the oral and ventral suckers. In the depth of the oral sucker there is a mouth, which leads into a pharynx and esophagus; the latter runs into two blind intestinal tubes (ceca) with numerous diverticula. The testes and ovaries are also branched. The well-developed vitelline glands occupy the lateral sections of the parasite's body, converging in the posterior quarter. The rosette-shaped uterus lies between the ventral sucker and the ovary (Fig. 92). The shells of the yellow-brown operculated eggs are thickened at the poles; their dimensions are 0.130-0.145 by 0.07-0.09 mm.

*F. gigantica* attains a length of 33-76 mm, but is only 5 to 12 mm in breadth. The lateral edges of the fluke are almost parallel. The eggs measure 0.150-0.190 by 0.075-0.090 mm.



The definite hosts of fasciola flukes are man and numerous herbivorous animals including sheep, cattle, goats, hogs and horses. Normally these flukes inhabit the extra- and intrahepatic biliary ducts and the gall-bladder; abnormal locations are various organs and tissues (ectopic fascioliasis). The duration of the life span of this fluke in its definite host is

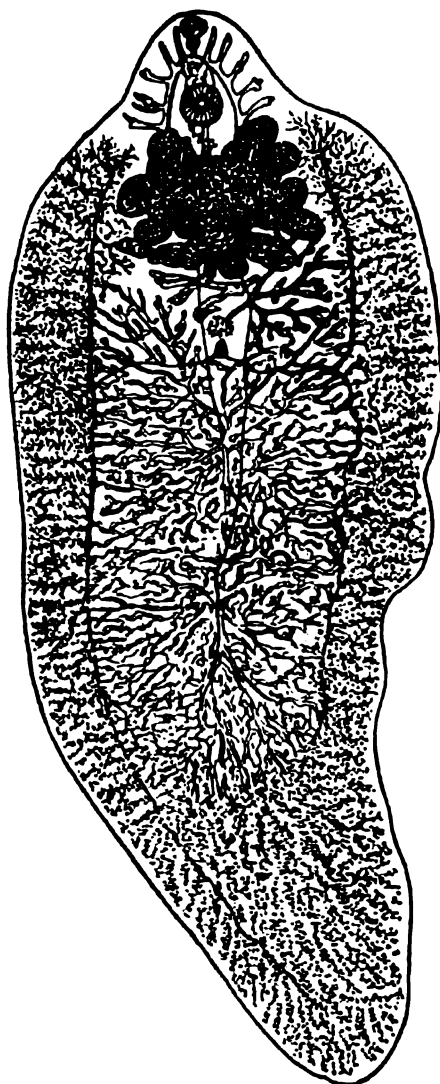


Fig. 92. *Fasciola hepatica*  
(L., 1758) (K. I. Skryabin  
R. S. Schultz)

not quite clear, but it is thought to be about 3 to 5 years. The intermediate hosts are various species of fresh-water snails, first and foremost of which is *Limnaea truncatula*.

### EPIDEMIOLOGY

The principal source of infection are fasciola-infested herbivores; the medical importance of human invasion is negligible.

The ova of these worms are voided with the feces of infested animals and man. In water or in moist soil a ciliate larva (miracidium) is formed in the ova within a period of 4 to 6 weeks or even longer. By this time the substance that holds down the operculum of the egg liquifies; the operculum opens and the miracidium swims out into the water where it penetrates into the body of a snail, the intermediate host. In the snail the parasite goes through an involved developmental cycle of larval generations that terminates in the formation and emergence of a blunt-tailed cercarial larva;

the cercaria soon sheds its tail, and then its cystogenic glands discharge a substance that envelops the larva and hardens, forming a closed capsule around it. The encapsulated cercaria is called an adolocercaria.

Man and other mammals become infested by ingesting the adolocercariae with water. Animals also acquire it by grazing on grass that grows in stagnant or slowly flowing waters.

Endemic foci of fascioliasis among animals are characterised by the presence of numerous snail-populated water bodies that serve as drinking places for cattle.

### GEOGRAPHICAL DISTRIBUTION

Although the distribution of fascioliasis is worldwide its incidence among human beings is not high and it is observed only sporadically; however, an outbreak of the disease involving 500 people has been described in France (Coudert a. Triozon, 1958).

### CLINICAL ASPECTS

The incubation period of fascioliasis is, according to different authors, from one to eight weeks. The first symptoms are malaise, progressive weakness, headache, loss of appetite; occasionally urticaria is observed and fevers are frequent. The latter may be of a remittent, undulating, or even hectic nature. In severe cases the temperature has been observed to go up to 39-40° C. Examination of the patient often reveals icteric sclera. Soon pains appear in the epigastric and right subcostal regions; nausea, sometimes vomiting are observed. The liver gradually enlarges, becoming firm and tender to palpation. A. M. Kryukov (1927) considers that the predominant enlargement of the left lobe of the liver, causing protrusion of the epigastric area and extension of this organ downward to the navel and leftward to the spleen is a symptom pathognomonic of fascioliasis. This hepatic enlargement occurs very rapidly and is accompanied by intense pain; as the attack subsides the liver is restored to its normal size just as rapidly. It must be pointed out that a similar phenomenon is observed not only in fascioliasis, but also in another liver helminthiasis—opisthorchiasis. The cause is probably the temporary derangement of bile circulation owing to complete or partial obstruction of the biliary ducts by the parasites.

The spleen is occasionally enlarged. Differential blood counts in the early stages of the disease show, as a rule, a marked eosinophil leukocytosis attaining 18,000-20,000 leukocytes with 85 per cent eosinophils. A case of eosinophil leukemoid reaction has been described in which the total leukocyte count was 52,000 and the eosinophil count was 40,560 per ml of blood (Mohr et al., 1951). With time the acute symptoms gradually subside, the temperature goes down to normal and subfebrile levels and the condition passes into a chronic phase. Dyspeptic symptoms and pains in the abdomen become prevalent. Sometimes the abdominal pains are

not very marked, the patient only experiences pressing or piercing sensations in the epigastric region and in the right subcostal area. However, these pains quite occasionally acquire a paroxysmal nature, of the type of gall-stone colic; they are accompanied by enlargement of the gallbladder, rises of temperature to 38° C and higher, sometimes with a subsequent development of a mild jaundice. The duration of these attacks varies greatly—from several hours to 7-8 days (D. T. Zhamyanova, 1949). There are no pains, or only very slight ones, in the periods between attacks. The liver usually protrudes 2-5 cm below the subcostal rim, but it is not always enlarged; it becomes hard, its surface remaining smooth. Blood tests show a normal white count, or moderate leukocytosis; the increase in eosinophils is usually not great (7-10 per cent).

Suppurative angiocholitis and abscesses of the liver caused by a secondary infection have been described in recent years by Moormann (1950) and P. T. Kazakov (1954). Cases of obstructive jaundice caused by a gigantic fasciola blocking the common biliary duct have also been reported (Stemmermann, 1953, and other authors).

Protracted duration of the disease may bring on marked dysfunctions of the liver (jaundice, etc.), diarrhea, macrocytic anemia, emaciation, and death (A. Kryukov, 1927). However, in the majority of cases fascioliasis is attended by mild clinical symptoms—slight dyspeptic disorders and dull pains in the abdomen.

An analysis of liver fascioliasis symptomatology shows that allergic symptoms are most forceful in the early stages of the disease, while angiocholitis (occasionally purulent), dyskinesia of the biliary tract, and occasionally hepatitis are manifested in later periods. The manifold clinical features of fascioliasis depend on the intensity of infestation (the greater the number of flukes in the biliary tract, the more severe the disease), on aggravating conditions (secondary infection, a concomitant disease, great physical exertions, deficient nutrition), and on individual peculiarities. Finally, ectopic fascioliasis must also be taken into consideration: the flukes have been discovered in the eye, under the skin, in the area of the larger curvature of the stomach, in an abscess of the appendix, in the portal vein.

Duga (1923) described a subhepatic abscess caused by the fasciola; Huvea observed a patient with feverish chills and hemoptysis who expectorated a gigantic fasciola. The discharge of fasciola flukes with the sputum has also been reported by Ulrich (1930), and Stemmermann (1953). A condition of so-called pharyngeal fascioliasis may develop following the ingestion of raw fascioliasic liver of cattle. The living flukes attach themselves by their suckers to the mucosa, causing edema of the pharynx, larynx, nasal cavity and auditory (eustachian) tubes. This may result in severe asphyxia threatening the patient's life.

## DIAGNOSIS

The diagnosis of fascioliasis is difficult in the early stages as the parasites commence oviposition only 3-4 months after penetrating into the human body. The condition must be distinguished first of all from trichinosis, a disease that is also accompanied by fever and a high eosinophil count. However, puffiness of the face and muscular pains are characteristic of trichinosis, while these features are absent in fascioliasis. In doubtful cases muscular biopsy is performed and the specimens are examined for trichinella larvae. Valuable aid may likewise be obtained by immunological reactions specific for fascioliasis and for trichinosis—the allergic cutaneous test, the precipitation and complement-fixation reactions.

When the flukes have already attained sexual maturity their discovery in the body is usually not difficult, as the characteristic ova of the parasite are demonstrable in the feces and duodenal fluid of the patient. However, it must be borne in mind that the ingestion of fascioliasic liver of cattle may lead to the appearance in the stool of so-called transitory fasciola eggs that pass unchanged through the human gastrointestinal tract. Cases are known when such eggs were found in the feces of people being treated perorally for pernicious anemia with liver extract. There are no reliable morphological features that might permit the differentiation of transitory ova from ova eliminated by the flukes in the patient's liver. It is therefore necessary in such cases to examine duodenal juice specimens, while the stool should not be examined earlier than one week after the complete exclusion of liver from the patient's diet (Fig. 93).

## PROGNOSIS

Prognosis is usually favourable with timely diagnosis and vigorous therapy. In severe cases, particularly in the presence of secondary infections, it may be bad.

## PATHOLOGY AND PATHOGENESIS

In the gastrointestinal tract the fasciola larvae ingested with food or drink emerge from their encapsulating membranes and penetrate into the hepatobiliary system, or, occasionally, into other organs or tissues. Current consensus of opinion is that the flukes migrate by two routes—through the blood, penetrating the blood vessels of the portal vein system, and through the peritoneum. In the latter case they work themselves through the intestinal wall into the abdominal cavity, moving toward the liver, penetrating into its parenchyma through Glisson's capsule, and then into the biliary ducts where they attain sexual maturity within 3 to 4 months. There can be no doubt that the activity of the young flukes during their migration inflicts mechanical damage on the tissues of the host. It is possible that the glands of the parasites secrete proteolytic substances that lyse the liver cells. Mechanical damage is also inflicted by the adult flukes as they

move along the biliary ducts and attach themselves to the walls of these ducts by means of their suckers; the walls of the biliary ducts are also injured by the spines on the anterior end of the flukes. Sometimes the parasites completely or partially obstruct the lumens of the ducts, inhibiting or arresting the flow of bile.

It is quite definite that the metabolic products of the helminths are allergens conditioning sensitisation; therefore the allergic symptoms are most vivid in the first phase of the clinical course of fascioliasis.

There can scarcely be any doubt that the combined mechanical and toxic effects of the fasciola flukes on the walls of the biliary ducts and gall-bladder irritate the nerve endings in them, causing the subsequent appearance of viscerovisceral reflexes affecting the function of various organs, first of all the gastrointestinal tract and the pancreas. This aspect of fascioliasis has, regrettably, received insufficient attention. The changes that occur in the walls of the biliary ducts and the derangement of the biliary flow create conditions favourable for a secondary infection. It is also quite probable that the fasciolas bring in bacteria from the intestine during their migration.

Proof of the infestation of the biliary tract with fasciola flukes is in some cases obtained by the recovery of microbes from the bile and the positive therapeutic response to antibiotics (e. g., biomycin).

Liver biopsy performed in the early phases of fascioliasis establishes the presence of microabscesses and micronecrosis with eosinophilic and giant cell infiltration. In later phases dilatation of the lumens, thickening of the walls, and adenomatous growth of the biliary tract epithelium occur; occasionally purulent angiocholitis develops; obliteration of the hepatic duct has also been described.

## **TREATMENT**

The principal agent currently employed in the treatment of fascioliasis is emetine hydrochloride; a 2 per cent aqueous solution of this preparation is injected subcutaneously or intramuscularly, 1.5 ml twice a day. Treatment is given for 3 days, followed by a 4-day interval, and then another 3-day course of emetine. Four or five courses are administered, sometimes even more, depending on the therapeutic effect. It is permissible to prescribe emetine in 6-day courses with a 7-day interval between them; commonly 2-3 such courses suffice. Recommended daily dosages for children and adolescents: younger than one year 0.005 g; from one to two years 0.01 g; from three to five 0.015 g; from six to nine 0.03 g; from ten to fifteen 0.04 g. An 0.5-1 per cent solution may be used for children. Emetine solutions are prepared on cooled sterile water, boiling is not permitted. Frequent electrocardiography during treatment is very advisable, as the therapy may then be interrupted upon the appearance of myocardial symptoms. Secondary infections are treated with penicillin, streptomycin, or biomycin; the antibiotic of selection is the one to which the bacteria recovered from the duodenal juice of the given patient are most susceptible.

A. I. Perikhanyan and L. I. Zorabyan (1948), incorporating the experience of veterinary practice, proposed using hexachloroethane in the therapy of fascioliasis in man; this preparation is prescribed per os for one day, 2 g every 15 minutes, the total dose reaching 8 g (0.16-0.2 g/kg). D. Zhamyanova was successful with this preparation in dosages of 10 g on the first and second days and 5 g on the third day. I.A. Zimin and G. P. Smirnova (1951), I. I. Topuriya and O. P. Zenaishvili (1954) claim a good effect with a single 2.5-3 ml dose of carbon tetrachloride.

### **PROPHYLAXIS**

The prevention of fascioliasis is realised by abstaining from drinking unboiled water from stagnant and slowly flowing waters; the water, in extreme cases, should be filtered through canvas. To combat the disease in farm animals a system of therapeutic and prophylactic measures must be enacted: mass treatment of the infested animals with carbon tetrachloride and hexachloroethane, extermination of snails, dehelminthisation of manure, alternation of pastures, etc.

# FASCIOLOPSIASIS

---

Fasciolopsiasis is a helminthiasis that predominantly affects the gastrointestinal tract.

## HISTORICAL DATA

The causative agent was first described by Lankester in 1857. Its biology was clarified by Nakagawa in 1921.

## ETIOLOGY

The causative organism is the largest intestinal fluke of man, *Fasciolopsis buski* (Lankester, 1857) which belongs, together with *Fasciola hepatica*, to the *Fasciolidae* family. When alive the parasite is reddish-brown and its shape is lingual. The fluke measures 15 to 50 mm in length and 8.5 to 20 mm in breadth. Its integument is scaly-spined. The ventral sucker is much larger than the oral sucker. The intestinal tubes do not branch; the testes are large and dendritic. A small dendritic ovary lies in front of the testes. The elongated ova are 0.13-0.14 by 0.08-0.095 mm (Fig. 94).

The definite hosts of this fluke are man, pigs, wild hogs (the boar), and dogs; the parasite inhabits the small intestine and the stomach, occasionally penetrating into the liver and pancreas. Cases have been described when as many as 3,500 fasciolopsis flukes were found in the human intestine.

The intermediate hosts are fresh-water snails *Planorbis haemisphaerulus*, *P. schmackeri*, and others.

## EPIDEMIOLOGY

The principal source of infestation are man and domestic swine. The wild boar constitutes a natural reservoir of infection in India.

The eggs of these helminths are voided from the body of the definite host in the feces; when the eggs contact water a miracidium hatches from

each egg within 2-3 weeks; swimming around in the water the miracidia attach themselves to snails and penetrate into the bodies of these intermediaries. In the snail the larval generations of the fluke develop and multiply, until finally caudate cercariae are formed that emerge into the water,



Fig. 94. *Fasciolopsis buski*  
(Lankester, 1857) (K. I.  
Skryabin, V. P. Podyapol-  
skaya, N. A. Statirova)

where they attach themselves to water plants and encyst, becoming adolocercariae. Man acquires the infection by ingesting the adolocercariae attached to the fruit of the water-caltrop (*Trapa natans*) or to the tubers of the water-chestnut (*Eliocharis tuberosa*). Incidence is particularly high among people who peel the fruit with their teeth.

#### GEOGRAPHICAL DISTRIBUTION

Fasciolopsiasis is quite widespread in certain areas of South China, Thailand, and in India; it has been registered on Taiwan, in Vietnam, on the Philippines.

#### CLINICAL ASPECTS

Manifestation may be subclinical, mild, or severe. The latter forms are usually the result of a very heavy infestation and deficient nutrition. The symptoms most characteristic of severe forms are abdominal pains com-



monly unconnected with intake of food, and diarrhea with fetid stools containing particles of undigested food and no signs of blood. These loose stools alternate intermittently with normal stools and constipation. The eosinophil count may frequently be increased, and anemia is occasionally observed. The patient's weakness increases gradually, dizziness and somnolence appear.

In late phases of a progressive form of the disease edematous swelling of the lower extremities and in male patients also of the scrotum is noted; ascitic fluid accumulates in the abdominal cavity and general anasarca develops. The patient's skin becomes dry and pale yellow, his arterial pressure goes down; the temperature falls to subnormal levels. Hypoproteinemia is established in the blood. The patient is likely to succumb to emaciation and increasing weakness of the cardiovascular system. However, in some cases, even fatal ones, no edema is observed.

The pathogenicity of the fasciolopsis flukes was dramatically illustrated by the experimental self-infestation of Barlow, a researcher who ingested 132 adolocercariae of the helminth. Six weeks later epigastric pangs and a sensation of hunger developed. At times these symptoms disappeared, but then returned again. Later a mild diarrhea appeared, alternating with constipation. A severe diarrhea developed 11 weeks after infestation; the fetid, loose stool was passed as frequently as 6 times a day, and abdominal pain appeared. This condition continued for two weeks. A total of 124 fasciolopsis flukes were recovered following dehelminthisation with tetrachloroethylene.

In mild cases only dull pains in the abdomen and occasional loose stools are noted.

### **PATHOLOGY AND PATHOGENESIS**

Viranuvatti, Stitnimankarn, and Tansurat (1953) autopsied the body of a female patient who had succumbed to fasciolopsiasis. They found hyperemia of the mucosa proper and of the submucosal coats of the intestine and stomach, hyperemia of the lungs, liver, kidneys and spleen, diffused hemorrhages in the lungs, fatty degeneration of the liver and vacuolisation of the hepatic cells.

The fasciolopsis flukes parasitising the human intestine and stomach, at times in enormous numbers, damage the mucosa, causing gastritis, enteritis, derangement of the motor and secretory functions of the gastrointestinal tract. They also cause intoxication and sensitisation of the organism. The development of a secondary alimentary dystrophy with edema (the edematous form) or without it (the dry form) are possible results of protracted intestinal disorders. A great part in the onset of dystrophy is played by protein and vitamin deficiencies in the patient's diet.

## **TREATMENT**

Dehelminthisation is effectedd by means of tetrachloroethylene, heptyl-resorcinol, thymol, as in ancylostomiasis. Thymol causes the helminths to be eliminated with body defects (K. I. Scryabin et al., 1929). Barlow (1927) considers that the most effective treatment is the peroral administration of betanaphthol; the adult dosage is 1.5 g of the preparation 3 times a day over half-hour intervals; weak children are given 0.75-1.25 g of the preparation daily in three portions. In the presence of symptoms of alimentary dystrophy (hypoproteinemia, etc.) therapy aimed at systemic improvement should be carried out—a high protein and vitamin diet, blood transfusions, vitamins C, A, B<sub>12</sub>, folic acid, iron.

## **PROPHYLAXIS**

Fasciolopsiasis is combated by wide-scale planned dehelminthisation of patients and protection of water bodies against fecal contamination. Individual prophylaxis is effected by cooking the tubers and fruits of water plants at proper high temperatures, or by immersing them in a 20 per cent solution of table salt for 1½ hours, or in a 5 per cent solution for 3 hours.

## ECHINOSTOMIASIS

---

Echinostomiasis is a helminthic disease caused by various species of trematodes of the genus *Echinostoma* (Rudolphi, 1809). Infestation by *E. lindoense* and *E. ilocanum* are most frequently encountered in man.

1. *E. lindoense* (Sandgraund a. Bonne, 1940). The length of this fluke is 1.5 mm, its breadth 0.25 mm. The parasite carries an anterior collar comprised of 37 spines.

The definite hosts of this helminth are man and rats; it inhabits the small intestine. The first intermediaries are the snails *Asinus sarasinorum* and *A. convexiusculus*, the secondary intermediaries are other molluscs — *Viviparus javanicus rudipellis*, *Corbicula lindoense*.

Man acquires the infection by ingesting the secondary intermediate snail hosts of the parasite.

*E. lindoense* infestation is widespread on the island of Sulawesi (Celebes); 42 to 85 per cent of the population are infected in one of the local sites, where this parasite is the cause of abdominal pains and diarrhea.

The preparation used for treatment is tetrachloroethylene. The habit of eating raw shellfish should be abandoned in order to avoid infection.

2. *E. ilocanum* (Garisson, 1908). This fluke measures 4 to 6 mm in length by 0.75 to 1.35 mm in breadth. The anterior part of the cuticula is studded with spines. There is a cephalic collar consisting of 49-51 spines. The eggs are 0.088-0.111 by 0.053-0.074 mm.

The definite hosts of this fluke are man, rats and in experiments also cats and monkeys. It inhabits the intestine. The first intermediate host is the snail *Planorbis* (*Gyraulus*) *prashadi*. The secondary intermediaries are various other species of molluscs (*Pila lusonica*, etc.).

*E. ilocanum* has been found in man on the Philippines and Java. Infection is frequently contracted by eating raw shellfish. The pathogenesis and clinical features of the disease have not been studied. Dehelminthisation is effected with thymol and tetrachloroethylene. It is recommended not to eat raw shellfish.

Other echinostomata parasitic to man are the occasionally found *E. paraulum*, *E. revolutum*, *E. macrorchis*, *E. cinetorchis*.

## EUPARYPHIASIS

---

Euparyphiasis is a group of helminthic diseases caused by flukes of the genus *Euparyphium* (Diez, 1909). Infestation with *E. jassiense* and *E. malayanum* has been registered in man.

1. *E. jassiense* (Leon a. Ciurea, 1922) is 5.4 to 7.6. mm long and 1-1.3 mm broad. Its anterior collar consists of 27 spines of two sizes; the ova of this parasite measure 0.132-0.154 by 0.079-0.085 mm. The organism was first discovered in Rumania by Leon and Ciurea. Neither the life-history, pathogenesis, clinical aspect, nor epidemiology of this worm disease have been studied.

2. *E. malayanum* (Leiper, 1911) is a fluke 8-12 mm in length and 3-3.3 mm in breadth. It possesses an anterior collar consisting of 42-43 spines. The ova are 0.120-0.130 by 0.080-0.090 mm. The parasite has been discovered twice in man in Malakka. It causes chronic enteritis. Dehelminthisation is effected by means of male fern extract. The life-history of this fluke and, consequently, the epidemiology and prophylaxis of the disease it causes, are unknown.

## ECHINOCHASMIASIS

---

The pathogenic organism of this disease is *Echinochasmus perfoliatus* (Ratz, 1908). The fluke measures 3-4 mm by 0.7-1 mm, its collar consists of 24 spines, its ova are 0.1-0.11 by 0.05-0.079 mm.

The definite hosts of this parasite are man, dogs, cats; it inhabits the small intestine. The first intermediate hosts are snails of the genus *Parafossalurus*. Secondary intermediate hosts are various species of fish: the ide *Leuciscus idus*, the tench *Tinca tinca*, the bream *Abramis brama*, *Blicca bjoerkna* and others. Man becomes infested by consuming raw or semi-raw fish. The disease is encountered in man in Japan. It is attended by symptoms of enteritis. Dehelminthisation is effected with thymol, tetrachloroethylene, chenopodium oil.

# HIMASTHLOSIASIS

---

The causative organism is a trematode worm, *Himasthla müchlensi* (Vogel, 1935). This is a comparatively slender fluke, 11-11.7 by 0.4-0.67 mm. Its anterior collar consists of 32 spines. The irregularly elongated ova measure 0.114-0.149 by 0.062-0.085 mm.

The parasite was discovered by Vogel in the stool of a patient who had come to Germany from America. The life-history of this helminth is unknown, no study has been made of the clinical features of the disease it causes.

## GASTRODISCIASIS

---

Gastrodisciasis is a morbid condition caused by infestation with the amphistome trematode *Gastrodiscoides hominis* (Lewis a. McConnell, 1876). The living parasite is reddish-orange in colour, its body is pear-shaped, measuring 4 to 10 mm in length and 3 to 6 mm in breadth. The dorsal surface of the body is convex, the ventral surface in the posterior discoid part is concave. A powerful ventral sucker, four times the size of the oral sucker, is situated in the caudal portion of the body. The esophagus runs into two symmetric diverticula; the lobulated testes lie centrally in front of the ovary. The uterus is short, the vitelline glands are situated in the lateral parts of the body. The operculated ova have assymetric bulges in their shells opposite the operculum; their dimensions are 0.150-0.157 by 0.06-0.072 mm.

Man and swine are the definite hosts of this helminth; localisation of the parasite is in the cecum. The intermediate hosts are molluscs, probably *Cleopatra bulinoides* snails. The definite hosts evidently contract the infection by drinking water or ingesting vegetable food contaminated with the encysted larvae that emerge from the snails.

*Gastrodiscoides hominis* was discovered in man by Stimson in India in 1857. It was subsequently found in Indo-China, the islands of Indonesia, and in British Guiana. Tetrachloroethylene and thymol are used for de-helminthisation.

# PLAGORCHIASIS

---

Plagiorchiasis is a morbid condition caused by flukes of the genus *Plagiorchis* (Lühe, 1899).

The species discovered in man include *P. philippinensis* (Sandground, 1940); *P. javanensis* (Sandground, 1940); *P. muris* (Tanabe, 1922). The first of these flukes was discovered by Africa and Garcia in 1935 at a post-mortem examination in Manila; the second was found by Sandground in a native of Java in 1940. McMullen infested himself with *P. muris* by ingesting larvae recovered from shellfish.



## **WATSONIASIS**

---

This is a morbid condition caused by infestation with the amphistome fluke *Watsonius watsoni* (Conyngham, 1904). The body of the parasite is pear-shaped, yellowish-red, measuring 8-10 by 4-5 mm. The elongated ova are 0.122-0.130 by 0.075-0.080 mm. This fluke was discovered in 1904 by Watson in the small intestine of a Negro of West Africa who had succumbed to a severe condition of profuse diarrhea and cachexia.

Snails are the presumable intermediate hosts of this fluke.

## EURYTHREMASIASIS

---

The causative agent of this disease is a parasitic worm, *Eurythrema pancreaticum* (Looss). Its body measures 15 to 18 mm in length and 6 to 8 mm in breadth. The oral sucker is much larger than the ventral sucker. The testes are lateral to the ventral sucker in front of the ovary, the vitelline glands lie in the third quarter of the body; the uterus occupies the caudal part of the worm. Its ova are indistinguishable from the ova of the lanceolate fluke *Dicrocoelium lanceatum*; they measure 0.044-0.048 by 0.032-0.036 mm.

The definite hosts of *Eurythrema pancreaticum* are man, large and small horned cattle, swine. The parasite concentrates in the pancreatic ducts. In man it has been discovered once in Siang Yang. Neither the pathogenesis nor clinical features of the disease are known. In animals a chronic or, occasionally, even an acute necrotic pancreatitis develops. Therapy and prophylaxis have not been studied.

# SPARGANOSIS

---

Sparganosis is the infestation of man by pleurocercoid larva of tapeworms.

## ETIOLOGY

The pathogens of the disease are *Diphyllobothrium erinacei-europei* (Rudolphi, 1819), *D. (Sparganum) proliferum* (Ijima, 1905), and possibly, also other species of tapeworms.



Fig. 95. *Diphyllobothrium (Sparganum) proliferum* (Stiles)

*D. erinacei-europei* (synonyms: *D. mansonii*, *D. decipiens* and others) is a large tapeworm attaining in its stage of sexual maturity a length of 250 cm, while its breadth does not exceed 12 mm.

The definite hosts of the tapeworm are cats, dogs, foxes, wolves, leopards, tigers; it infests the small intestine of these animals. The first intermediate hosts are *Mesocyclops leuckarti* and other copepods. The helminth

has as its secondary intermediaries various species of frogs, snakes, birds, mammals, and also man; the pleurocercoids of this tapeworm infest various organs and tissues of the bodies of their secondary intermediate hosts. They measure 8 to 60 cm in length and 2 to 3 mm in breadth.

*Sparganum proliferum* is 3-12 mm long and 2.5 mm broad. The adult form of this helminth is unknown (Fig. 95).

### EPIDEMIOLOGY

Man contracts sparganosis (*D. erinacei*) by ingesting infected copepods with water, and by eating frogs and snakes. In some countries it is customary to apply frogs as poultices for curing skin and eye diseases; the infection is acquired by contact with frog flesh—the pleurocercoids of the tapeworm emerge from the frogs and penetrate the human integuments. The developmental cycle of *Sparganum proliferum* is not known.

### GEOGRAPHICAL DISTRIBUTION

The highest incidence of sparganosis has been reported from the countries of the Far East; it has been registered in Australia, Africa, the U.S.A., South America, Holland.

### CLINICAL ASPECTS

The most frequent site of infestation is the eye; the symptoms are pain, watering, edema and ptosis of the lids. Infestation of the subcutaneous tissues and muscles causes itching, nettle-rash, a sensation of movement of the worm, the formation of nodules and occasionally of abscesses. The spargana have also been discovered in the visceral organs—in the intestinal walls, kidneys, bladder, urethra, on the pleura, in the pulmonary artery. *Sparganum proliferum* proliferates into the tissues of the host by branching and budding off large numbers of spargana (in the muscles, subcutaneous tissues, lungs, brain, kidneys, heart). As a result the intensity of infestation increases excessively, abscesses of the skin and of the subcutaneous layers are formed, as well as severe lesions of the viscera—the kidneys, heart, brain, etc.

### DIAGNOSIS

The diagnosis of sparganosis is based on the demonstration of the worms removed by surgical operations.

### PROGNOSIS

Prognosis may be unfavourable in cases of infestation of the viscera.

## **TREATMENT**

The most advisable treatment is surgery. If this is unfeasible then neosalvarsan (novarsenol) is administered; this preparation is injected intravenously in doses of 0.3-0.45 g over intervals of 4-5 days (Manson-Bahr, 1954).

## **PROPHYLAXIS**

The only prophylactic measures are to drink no unboiled water, or at least to filter it through canvas, to consume no raw or partly cooked birds, frogs, snakes, and not to apply frog meat poultices to any part of the body.

## BERTIELLIASIS

---

Definition: a morbid condition caused by the tapeworm *Bertiella studeri* (Blanchard, 1891). Synonym: *B. satyri*. The body of this tapeworm reaches 115 cm in length and is 15 mm broad. The scolex carries a rudimentary rostellum and four suckers. The eggs measure 0.045 by 0.05 mm. The embryo (the oncosphere) in the egg possesses a peculiar rudimentary pear-shaped apparatus. The site of infestation is the small intestine of man. Infection is acquired by the accidental ingestion of armoured ticks of the *Aribatidae* family, the intermediate hosts to the parasite. Bertielliasis has been reported in India, on the islands of Mauritius, Java, Sumatra, and the Philippines.

The clinical features of the disease are not clear. Diagnosis depends on recovery and identification of the ova from the feces.

## RAILLIETINIASIS

---

A group of morbid conditions caused by tapeworms of the genus *Raillietina* (Fuhrmann, 1920), family *Davaineidae*. The strobila of these cestodes consists of numerous proglottides; the rostellum carries two rows of hooks, and the suckers are also armed with hooklets; the genital pores are either unilateral, or are placed in an alternate lateral order. The length of various species of *Raillietina* varies from 20 cm to 5 m. The worms inhabit the small intestine of man. They have been reported from South America, Thailand, the Philippines, Java, and Taiwan; sporadic cases have been registered in the U.S.S.R. (Ashkhabad, Armavir). The clinical features, epidemiology, and prophylaxis are not known.

## ANCYLOSTOMIDOSES (HOOKWORM DISEASES)

---

Ancylostomidosis is a term incorporating two worm diseases caused by pathogenic hookworms possessing very close biological features—ancylostomiasis and necatoriasis; the pathogenesis and clinical aspects of these diseases are very similar and they are often observed simultaneously. The prevalent site of infestation is the gastrointestinal tract, with frequent hypochromic microcytic (iron deficiency) anemia.

Ancylostomiasis was discovered by Dubini in Italy in 1838. In 1854, Griesinger established that infestation with ancylostoma worms was the cause of a disease widespread in Africa and known as Egyptian chlorosis. This helminthiasis attracted particular attention in 1880, when an outbreak of severe anemia occurred among the men building the Saint Gothard tunnel. Perroncito proved the connection between the anemia and hookworm infestation. It was subsequently proved that this type of anemia may likewise be caused by infestation with hookworms of the genus *Necator*, first described in the U.S.A. by Stiles in 1902.

### ETIOLOGY

The causative agents of ancylostomidoses are nematode worms of the family *Ancylostomatidae* (Looss, 1905): *Ancylostoma duodenale* (Dubini, 1843); *A. braziliense* (De Faria, 1910), and *Necator americanus* (Stiles, 1902).

The hookworm *A. duodenale* is pink when alive and greyish-white when dead. The mouth end of the body is bent dorsally. The scolex carries a buccal capsule with four sharp hooked ventral teeth and two smaller sharp dorsal teeth. The male measures 8-11 mm by 0.4-0.5 mm, the female 10-18 by 0.4-0.6 mm (Fig. 96). The elongated ova are covered with a thin, transparent colourless shell; their dimensions are 0.054-0.07 by 0.036-0.04 mm; the fresh-laid ova contain 4 blastomeres in their central part.

The buccal capsule of *A. braziliense* carries two different pairs of ventral teeth. The male is 8.5 mm long, the female 10.5 mm.



*N. americanus* possesses less developed mouthparts as compared with ancylostome worms. The buccal capsule of this hookworm contains two sharp cutting plates and dorsally two projecting ventral pairs of teeth. The male measures 5.2-10 mm by 0.18-0.24 mm, the female 7.7-13.5 mm by 0.38-0.45 mm. The ova resemble those of the ancylostoma; their dimensions are 0.064-0.076 by 0.036-0.04 mm.

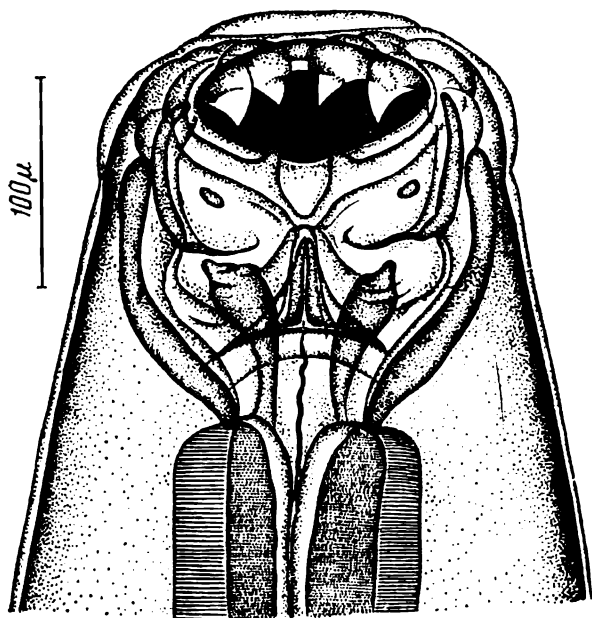


Fig. 96. *Ancylostoma duodenale*. Cephalic end with mouth capsule (K. I. Skryabin, R. S. Schultz)

Both species inhabit the small intestine, chiefly the duodenum and jejunum. They feed prevalently on blood, punching small wounds in the intestinal mucosa with the chitinous weapons in their buccal capsules. The cephalic and cervical glands of the worm discharge specific anticoagulants that protract the bleeding caused by the bites.

The life-span of the ancylostoma and necator in the human body is not known definitely. Apparently, these worms live for 3-5 years or even longer. Palmer (1955), observing an experimentally infested volunteer, established that the last necator perished 15 years after the infestation. The majority of *Ancylostomatidae*, however, die one or two years after penetrating the human body.

#### EPIDEMIOLOGY

The source of ancylostomidoses are infested people who void the ova of these hookworms in their stools. In favourable conditions of moisture and temperature a larva is hatched from the egg in 24 hours; this larva moults twice, and in 5 days it becomes infestive, i.e., it acquires the ability of penetrating the human body and developing there into an adult form. The maturation of *Ancylostomatidae* ova in the outer environment is possible at temperatures between 14 and 37°C, and in localities where there is no less than 1,800 mm of rainfall annually. N. G. Kamalov (1946, 1949) states that in the Georgian Republic the eggs are capable of developing even at 5°C, on condition that there are short jumps to 15-17°C. At 0° the *Ancylostomatidae* ova are destroyed in the soil within one week. Conse-

quently, the propagation of ancylostomidoses is possible only in areas with a sufficiently warm and humid climate. In temperate zones favourable conditions for the preservation and development of the ova and larvae of hookworms in the outer environment exist only in moist mines where the temperature is 15 °C and higher. The hookworm larvae actively penetrate into the human body through the skin, and passively by ingestion with food and drink. Infestation occurs on contact with soil and grass contaminated with crawling larvae, and also by eating food contaminated with infestive matter (this pertains principally to vegetables) and by drinking contaminated water.

Upon penetrating the skin the larvae migrate to the lungs from whence they pass into the pharynx and mouth, where they are swallowed and thus delivered into the stomach and intestine. Within 3 to 5 weeks the larva attains sexual maturity. The larvae swallowed with food and drink develop in the intestine without any preliminary migration.

### **GEOGRAPHICAL DISTRIBUTION**

Ancylostomidoses are most widespread in tropical and subtropical areas where the soil is considerably contaminated by fecal matter, and also in places where nightsoil is used for fertilisation of vegetable gardens and plantations.

Hookworm infestation is very common to a number of tropical and subtropical countries where a total of approximately 500 million people are infested annually (a quarter of the entire population of the globe). Ancylostomiasis is also encountered in temperate zones, but exclusively among people occupied in warm, moist mines (Fig. 97).

### **CLINICAL ASPECTS**

The early clinical symptoms following penetration of hookworm larvae through the skin are connected with the migration of the larvae. Brumpt (1952) showed that within one or two days after primary infestation the patient develops an itch and erythema with small red papules. In 10 days these eruptions disappear. A second infestation provokes urticaria as soon as the hookworm larvae are placed on the skin; this condition subsides in several hours, after which red papules appear; they have diameters of 1 to 2 mm and are separated by areas of normal skin. When the same person is infested a third or fourth time the local lesions become more and more intense and are accompanied by local swellings and the formation of blisters.

Brumpt did not observe eosinophil infiltration of the lungs in his patients, a symptom that was noted in the early stages of ancylostomidoses by certain authors; however, four days after infestation he registered symptoms of involvement of the upper respiratory tract: a dry cough and hoarseness that even developed into complete aphonia. These symptoms persisted for approximately three weeks. Abdominal pains, vomiting, diarrhea

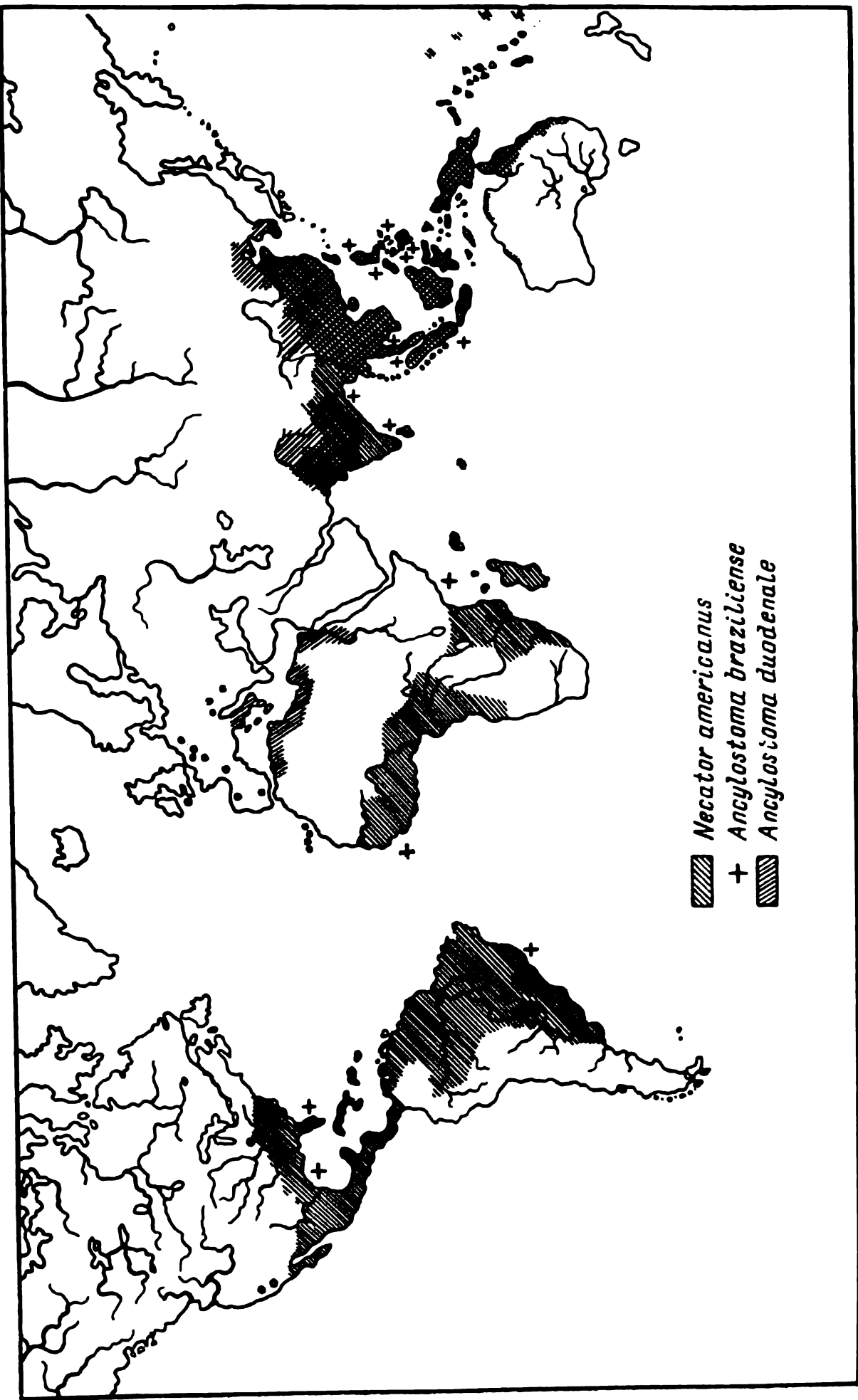


Fig. 97. Geographical distribution of ancylostomides (Faust, 1949)

and general malaise appeared in some patients 8 to 30 days after infestation. The epigastric pains prominent in numerous cases of ancylostomidosis are very similar to the pains attending duodenal ulcers. These pains are caused by duodenitis (including erosive duodenitis) and pylorospasm. N. G. Kamalov and M. N. Tzutzunava (1952) reported that the pains are most acute at the onset of the disease, abating subsequently. The most characteristic feature of ancylostomidosis is hypochromic anemia which occurs in the majority of patients, sometimes in a very severe form. Patients so afflicted complain of general weakness, dyspnea, a buzzing in the head, rapid physical and mental fatigue, dizziness, dimmed vision, weight losses, loss (or, in rarer cases, increase) of appetite. They often consume clay, chalk, coal, ashes, brick, and paper, and lick metals, salt, and soap (M. S. Gigitashvili, 1956).

Prominent symptoms are pallor of the skin, puffy face, occasionally edemas on the lower extremities. In many ancylostomidosis sites the skin of the patients acquires a yellowish hue; formerly many authors looked upon this sign as one of the most specific features of ancylostomidosis. However, Kamalov and Tzutzunava (1952) proved this yellowness to have nothing in common with ancylostomidosis; it is merely the result of a high carotene level in the blood. Carotenes (the precursors of vitamin A) are abundant in corn, carrots, citrus fruits. Therefore yellowness of the skin is observed in areas where the staple foods of the population are corn and other vegetables. Its incidence is the same both in ancylostomidoses patients and in people free of these worm diseases.

The temperature is usually normal or subfebrile, only rarely rising to 38° and higher.

The blood shows decreases in the hemoglobin value, red blood count, and colour index. In some cases the hemoglobin may fall to 8 g%, the erythrocyte count to less than one million, and the colour index to 0.3-0.5. Blood smears show anisopoikilocytosis, microcytosis, hypochromasia, and polychromasia of the erythrocytes. The number of reticulocytes is usually increased. The leukocyte count is somewhat lower than normal; eosinophilia is frequent, while in severe cases eosinopenia and even complete absence of eosinophils in the circulating blood are noted. Micronormoblastic regeneration is observed in the bone marrow (I. I. Topuriya, 1956). The total amount of blood is normal, but the plasma mass increases; blood viscosity is decreased; the ESR is accelerated. Arterial blood pressure is slightly decreased, blood circulation is accelerated (M. S. Gigitashvili, 1956).

Cardiac findings include a systolic murmur at the apex, occasionally a slight expansion of the contours of cardiac dullness, tachycardia.

In over 50 per cent of patients gastric acidity is lowered, even to complete achylia; however, occasionally acidity is increased (in 15 per cent of cases). Radiography of the stomach frequently demonstrates a delay in the propulsion of the radiopaque substance from the stomach into the intestinal tract, occasionally protracted pylorospasm is noted—a condition that may in some cases simulate pylorostenosis (M. N. Tzutzunava, 1952).

Enlargement of the liver and spleen are rare. Children and adolescents afflicted with ancylostomidoses are physically and mentally retarded, sexual maturation is late. In women oligo-, hypo-, or even amenorrhea, as well as early menopause, are not uncommon.

Characteristic psychic symptoms are dullness, apathy, loss of interest in the environment, decreased mental capacities, somnolence or insomnia.

The severity of the ancylostomidosic anemia depends on the number and, to a certain degree, also the species, of helminths, on the duration of the infestation, and the quality of the patient's ordinary diet.

Yokogawa (1937) showed that the changes occurring in the blood during infestation with the *Ancylostoma* and *Necator* hookworms are generally the same, but in *A. duodenale* infestation the onset of the anemia is more rapid and severe than in infestation by *N. americanus*.

The pathogenicity of *A. braziliense* is moderate. Observations of the blood of experimentally infested volunteers enabled Yokogawa to establish that the anemia usually appears 10 to 20 weeks after infestation and then gradually increases. The clinical observations made by Topuriya (1956) also show that the longer the duration of the infestation, the more severe the anemia.

Basophilic stippling and polychromasia of the erythrocytes and an increased reticulocyte count may occasionally appear in the early stage of anemia, 5 to 15 weeks after infestation, but with the progressive intensification of the severity of the disease the number of these cells decreases.

One to two weeks after oral infestation the leukocyte count starts going up, attaining its peak by the fifth or sixth week, and then returning to normal by the eighth or ninth week. In the tenth-twelfth week a second temporary rise in the white blood count may occur. The same pattern is observed in cases of cutaneous infestation, only the leukocytosis occurs a week or two later.

Eosinophilia becomes apparent one week (occasionally even three days) after infestation with *Ancylostoma*, attaining its maximum by the 5th or 9th week and then gradually decreasing. In some cases a temporary second rise in the eosinophil count may occur. The dependence of the severity of the anemia on the heaviness of infestation was demonstrated by G. P. Smirnova et al. (1949); these authors observed 500 necatoriasis cases. The severity of the anemia in the patients increased with the worm load; in the presence of 50-100 *Necator* worms the hemoglobin was 50-60 per cent, while infestation with 500-1,000 worms caused the hemoglobin values to become as low as 8-20 per cent.

However, it is not always possible to establish a direct relationship between the number of ancylostomides infesting a patient and the degree of anemia. Thus F. F. Soprunov (1950) could not detect it; he considers that in certain ancylostomidoses sites the patients are freed of a significant part of the worms as a result of their natural destruction by the time the anemia sets in. Consequently, anemia is in such an event only evidence of a higher degree of infestation in the recent past. Naturally, individual traits and the patient's nutrition are very important factors.

## DIAGNOSIS

Diagnosis of ancylostomidoses is based on a summarised analysis of clinical and laboratory data. The decisive factor is examination of the feces for hookworm eggs. It must be remembered, however, that these eggs are very similar to the eggs of *Trichostrongylus* worms; the only difference is the presence in the latter of 16 to 30 blastomeres.

## PROGNOSIS

Prognosis is favourable with timely diagnosis and prompt institution of therapy, but a fatal termination is possible in severe, neglected forms of anemia.

## PATHOLOGY AND PATHOGENESIS

During the migration of the larvae polymorphonuclear leukocyte infiltration of the tissues of the skin occurs, later fibroblastic, lymphocytic, and epithelioid infiltrations appear. In the lungs there are hemorrhages and eosinophil infiltrations. Infestation of the intestines results in a catarrhal condition of the mucosa, bleeding, occasionally erosion and even ulcers. A leading factor in the pathogenesis of ancylostomidoses is sensitisation of the organism by metabolic products and traumatic effects of the larval and adult hookworms on the tissues. The anemia many ancylostomidosis patients develop is the result of iron deficiency caused by prolonged hemorrhages. It has been computed that in the presence of 2,000 hookworms the body loses approximately 100 ml of blood a day. It may likewise be assumed that in certain cases the anemia is aggravated by a lowered assimilation of iron due to pathological changes in the intestine and to achylia gastrica. Sometimes the decisive factor in the onset of anemia is a diet faulty in iron, proteins and vitamins, and also (in women) the increased expenditure of iron during lactation.

## TREATMENT

Therapy in cases of ancylostomidoses without anemia is restricted to dehelminthisation alone. The presence of anemia requires a combination of dehelminthisation with specific therapy. In marked and severe forms of anemia (less than 40 per cent hemoglobin) pathogenetic therapy should be carried out before the administration of the anthelmintic.

Preparations of iron are administered in the pathogenetic therapy of ancylostomidosic anemia. Reduced iron (ferrum reductum) or iron carbonate (ferrum carbonicum) are prescribed in dosages of 0.5-1 g three times a day 30 minutes after meals; these preparations must be washed down with hydrochloric acid. A tincture prepared with malate of iron (tinctura ferri pomati) may likewise be prescribed, in 15-20-ml doses 3 times a day. A good effect is obtained by the combination of iron preparations with

campolon or antianemin, 2 ml intramuscularly every day or on alternate days, or by the prescription of vitamin B<sub>12</sub>, 15-30 micrograms twice a week.

Blood transfusions are indicated for particularly severe cases. Hookworm dehelminthisation is effected with tetrachloroethylene, chenopodium oil, thymol, heptylresorcinol, and alcopar (bephenium hydroxynaphthoate). On the days of tetrachloroethylene therapy and for a day or two before and after treatment the patient is not allowed any fats or alcoholic drinks; a carbohydrate diet is prescribed. Emaciated patients should be given calcium chloride, vitamin C, and pressed curds (cottage cheese) for two or three days prior to treatment. The preparation is administered 2-3 hours following a light breakfast (a glass of sweet tea and 100 g of white bread) in a single dose (in gelatin capsules or in 50 ml of water). In the latter case it must be measured out rapidly with a pipette to avoid evaporation. Thirteen minutes after the tetrachloroethylene has been ingested the patient is given a saline cathartic, and two hours later—lunch.

Single doses of tetrachloroethylene for the different age groups: from 3 to 5 years 0.5-0.6 ml; 6 to 7 years 0.8-0.9 ml; 8 to 10 years 1-1.5 ml; 11 to 15 years 1.5-2 ml; 16 to 20 years 2-3 ml; from 21 to 50 years 3 ml, and for patients of 51 years and older 2.5 ml.

In cases of concomitant hookworm and roundworm (ascarid) infestation tetrachloroethylene may be given only 12 to 14 days after successful dehelminthisation of the ascarids. Tetrachloroethylene may also be combined with chenopodium oil: 1-1.5 ml is mixed in water or skim milk with 1.5 ml of chenopodium oil and given to the patient in a single dose; a saline cathartic is administered 15 minutes later.

Contraindications for tetrachloroethylene are diseases of the liver and kidneys, acute gastrointestinal disorders, decompensation of the cardiovascular system, alcoholism, the combination of ancylostomidosis with ascariasis.

Tetrachloroethylene is administered in the same doses and manner as carbon tetrachloride (tetrachloromethane), to which it is closely allied.

Chenopodium oil is given two hours after a light breakfast together with 30-40 ml of castor oil, or 100-150 ml of a 30 per cent solution of sodium sulfate (Glauber's salt) or magnesium sulfate (Epsom salt). For adults chenopodium oil is prescribed in single 2-ml doses, the dosages for children and adolescents are as follows: 2 to 3 years 0.1-0.2 ml; 4-6 years 0.3-0.4 ml; 7-8 years 0.5 ml; 9-11 years 0.75 ml; 12-13 years 1 ml; 15-16 years 1.25-1.5 ml. The preparation is prescribed in capsules or measured with a pipette, and then thoroughly mixed with a cathartic (preferably castor oil) and given in one dose. The patient has his lunch 3 hours later. Upon retention of the stool an enema is given, or an additional dose of cathartic.

Contraindications for chenopodium oil are: diseases of the liver and kidneys, ulcerative and acute inflammatory diseases of the gastrointestinal tract, cardiovascular decompensation, diseases of the central nervous system, pregnancy, emaciation. Possible side effects are nausea, vomiting,

abdominal pain, slow pulse. Chenopodium oil treatment may be repeated no earlier than in one or two months.

Rp. Ol. chenopodii 0.5  
D.t.d. No. 4 in caps. gelat.  
S. To be taken after a light breakfast

Rp. Ol. chenopodii 2.0  
Ol. ricini 40.0  
MDS. To be taken after a light breakfast

Preliminary preparation of the patient for thymol treatment is the same as for the other above-indicated medications. It is prescribed in pulverised form, mixed with sugar. The patient takes it on a fasting stomach in powders or wafers. Daily doses of thymol: patients aged 2 to 5 years are given 0.2 to 0.5 g; 6 to 8 years 0.6-0.8 g; 9 to 10 years 1-1.2 g; 11 to 15 years 1.3-2 g; 16 to 20 years 2.5-3 g; 21 to 50 years 4 g. Patients older than 51 years receive 3 g.

The daily dose is divided into 4 portions given over 15-minute intervals. An hour and a half after the last portion has been taken a saline cathartic is administered. Lunch is served after the cathartic has been effective. This treatment is repeated on three consecutive days.

Rp. Thymoli 0.5  
D.t.d. No. 8 in caps.  
S. 2 wafers every 15 minutes per os

Contraindications for thymol administration are cardiovascular decompensation, diseases of the liver and kidneys, ulcerative and acute gastrointestinal diseases, pregnancy, emaciation, advanced age. Possible side effects: vomiting, diarrhea, cardiac weakness, acute intoxication (as with alcohol). In such cases gastric lavage is done, the patient is given a cathartic and enema, cardiac drugs and glucose are prescribed.

Treatment may be repeated in two or three weeks, but no more than 2-3 times a year.

Heptylresorcinol is prepared commercially in coated tablets containing 0.1 g. On the evening preceding treatment the patient is given a saline cathartic. The preparation is administered on an empty stomach, 1-2 tablets every five minutes. Three hours later lunch is served; in the evening or next morning the patient takes a saline cathartic. Single doses of heptylresorcinol for adults contain 1.5 g (15 tablets); children younger than 10 years are given as many tablets (0.1 g per tablet) as they number years of life; children of 11-13 years receive 1.2 g (12 tablets), adolescents of 14-15 years get 1.3 g (13 tablets).

Rp. Heptylresorcini 0.1  
D.t.d. No. 15 in tabul.  
S. All tablets to be swallowed uncrushed on  
fasting stomach within 30 minutes

Heptylresorcinol is contraindicated by ulcerative and acute diseases of the gastrointestinal tract and by debility. The treatment may be repeated in 2-3 weeks.



Alcopar (bephenium hydroxynaphthoate) is prescribed for adults and children older than 5 years in doses of 5.0 g; children younger than five years are given 2.5 g in a single dose. Cathartics are administered only in cases of constipation. Treatment is administered on 2 to 5 successive days.

### PROPHYLAXIS

Ancylostomidoses are combated by the planned mass treatment of patients, institution of general sanitary measures aimed at avoiding fecal contamination of the soil, and by proper individual hygiene.

In order to avoid diffusion of ancylostomidoses in mines all employees newly engaged for underground work are examined for worm diseases. Those infested with hookworms are permitted to work only on the surface until they have been cured. Extermination of ancylostomid larvae in the soil is effected by sprinkling the soil with ordinary salt, 0.5 to 1 kg per sq. metre every 5-10 days (N. G. Kamalov and S. M. Bugianishvili, 1949). F. F. Soprunov and N. Y. Soprunova (1953) proposed a method for dehelminthisation of the soil by the introduction of spores of carnivorous fungi of the genus *Didymozophaga* that exterminate nematode worms.

Individual prophylaxis consists of thoroughly washing vegetables and fruits and scalding them with boiling water before eating them raw; in endemic sites of ancylostomidoses it is not advisable to walk barefoot or to lie on the bare ground.

## FILARIAL DISEASES (FILARIASIS)

---

Filariasis is a morbid condition produced by infestation with filariae, long filiform nematodes belonging to the suborder *Filariata* (Scryabin, 1915). Man is the definite host to these parasites. The adult worms live in the lymphatic system, subcutaneous connective tissue, or serous cavities of the host, while the larval forms, or microfilariae, are commonly found in the circulating blood or they accumulate in the superficial layers of the skin.

The intermediate hosts of filariae, the vectors of the disease, are various species of bloodsucking arthropods. Filariasis is common among the population of a number of tropical and subtropical countries. The principal filariasis diseases of man are wuchereriosis, onchocerciasis, loiasis and acanthocheilonemiasis (Fig. 98).

### WUCHERERIOSIS

Wuchereriosis is a helminthic disease predominantly characterised by lesion of the lymphatic system, a condition that in late stages may cause elephantiasis of various parts of the body.

#### Etiology

The causative agent of wuchereriosis is *Wuchereria bancrofti* (Cobbold, 1877) and *W. (Brugia) malayi* (Brug, 1927) (Rao a. Maplestome, 1940).

*W. bancrofti* is a milk-white filarial parasite. Its body tapers at both ends. The male measures approximately 40 mm in length and 0.1 mm in breadth, the female 80-100 mm and 0.24-0.3 mm.

Man is the definite host to this parasite; the adult wuchereriae inhabit the lymphatic vessels and nodes, the microfilaria are located in the lymph and blood.

The adult female worm gives birth to microfilariae that migrate from the lymphatics to the blood. During the day they stay in the blood vessels

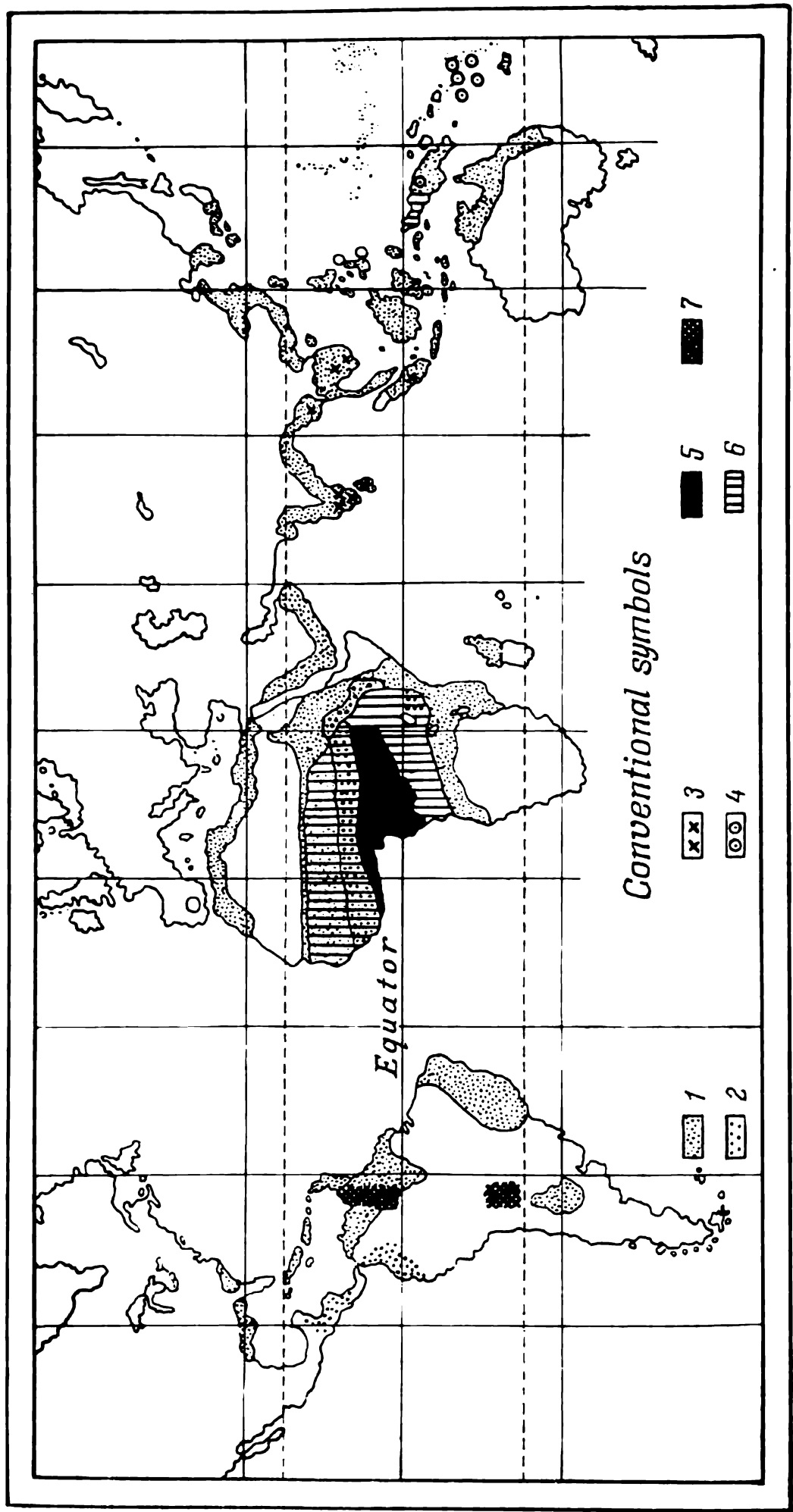


Fig. 98. Geographical distribution of filarial diseases of man (Manson-Bahr, 1945)

1 — *Wuchereria bancrofti*; 2 — *Onchocerca volvulus*; 3 — *Wuchereria malayi*; 4 — *Wuchereria pacifica* (a form in which the periodic emergence of the larva into the peripheral blood vessels is absent); 5 — *Loa loa*; 6 — *Acanthocheilonema perstans*; 7 — *Mansonella ozzardi*

of the lungs, heart, and muscles, in the aorta and carotids; during the evening and at night they migrate to the peripheral vessels, thus earning for themselves the name *Microfilaria nocturna*. The periodicity of the appearance of the microfilariae in the blood depends on the round-the-clock rhythm of physiological activities of the host. If the latter changes his habits, sleeping by day and waking by night, the microfilariae appear in the cutaneous vessels in the daytime instead of by night. Manson-Bahr (1941) described a so-called non-periodic strain of wuchereriae — *W. pacifica*, the microfilariae of which are found in equal amounts in the peripheral blood both in the night and during the day. The microfilariae recovered from superficial blood vessels measured 0.127 to 0.32 mm in length.

Adult wuchereriae live in the human body up to 17 years, the microfilariae live about 70 days.

The intermediate hosts of *W. bancrofti* are various species of blood-sucking insects of the genera *Culex*, *Aedes*, *Mansonia*, *Anopheles*.

*W. (Brugia) malayi* is a filariform nematode resembling *W. bancrofti*. The intertwined male and female inhabit the lymphatics. The body of this worm tapers at its anterior end. The rounded head is divided from the rest of the body by a neck. The male is 22-33 mm long and 0.088 mm broad; the female reaches 55 mm in length and 0.16 mm in breadth. The microfilariae are 0.165-0.265 mm long. The definite hosts are man and certain other primates (*Macaca iris*), cats and dogs. The adult forms inhabit the lymphatic system, the microfilariae are found in the blood. Mosquitoes of the genera *Anopheles* and *Mansonia* are the intermediate hosts.

### Epidemiology

The principal source of infestation are human wuchereriasis patients; the importance of certain monkeys, and of dogs and cats in the diffusion of *W. (Brugia) malayi* is only secondary. The vectors are mosquitoes in which the development of the microfilariae to the infestive stage takes 8 to 35 days, depending on the atmospheric temperature. Optimal conditions for their development are created at 21-32° C and 70-100 per cent humidity.

When a mosquito vector lights on a human victim the infestive microfilariae accumulated in the cutting apparatus of the insect emerge through a rupture in the membrane between the terminal lobes of its proboscis onto the human skin; upon penetrating the skin the larva finds its way to the blood stream and is carried to the site of infestation. The wuchereriae develop very slowly, attaining their adult stage in 3 to 18 months.

### Geographical distribution

Wuchereriasis is quite widespread in a number of areas of Africa, Asia, Australia, America.

In Africa it occurs indigenously in Egypt, Sudan, Kenya, Tanganyika, Nyasaland, Mozambique, Angola, Congo, Ruanda-Urundi, Cameroon, Nigeria, Liberia, Sierra Leone, Portuguese Guinea, Gambia, Morocco, on

the islands of Madagascar, Mauritius and others. Endemic sites of wuchereriosis have been registered in India, Burma, Thailand, Malaya, China, Korea, Japan, on the Philippines, in Indonesia; sporadic cases have been reported from Iran and Saudi Arabia.

This worm disease is quite common to certain localities of Australia and the islands of New Zealand, Fiji, Hawaii, New Caledonia, Cook, Ellice, the Solomons, the Bismarck Archipelago, etc.

In America wuchereriosis is endemic in Mexico, Brazil, Guatemala, Guiana. It has been registered in the southern states of the U.S.A. In Europe it has been observed in Spain (the vicinities of Barcelona) and Italy.

### **Clinical aspects**

The clinical symptoms of infestation with both species of wuchereriae are generally similar. The severity and symptomatology of these diseases vary exceedingly, from subclinical forms to intense suffering and even death. The incubation period of wuchereriosis is 3 to 18 months. Allergic symptoms are prevalent in the early stages of the disease. The patients develop fevers and erythematous painful eruptions appear on the skin, chiefly on the upper extremities; these eruptions resemble multiple exudative erythema; lymphangitis, funiculitis, orchitis, and bronchopneumonia are frequent developments.

The onset of lymphangitis (a condition often observed in later stages of the disease as well) is accompanied by the appearance on the skin of red cord-like swellings attended by regional lymphadenitis, fever, headache, anorexia and general malaise. It is not uncommon for lymphangitis in males to be associated with funiculitis—painfulness and thickening of the spermatic cord—and orchiepididymitis. In the latter case the testes and their appendages are enlarged and painful, the scrotum becomes erythematous and swollen. Prolonged relapsing courses of funiculitis and orchiepididymitis result in the formation of a hydrocele. Mastitis has been described in female patients.

During the second phase of the disease, 2 to 7 years after infestation, a varicose dilatation of the cutaneous and deep lymphatics occurs gradually. Rupture of the lymphatics in the kidneys and bladder lead to chyluria and hematochyluria, in the intestine to chylous diarrhea, in the peritoneum to chylous ascites, in the scrotum to chylocele. A lymph scrotum develops in some patients: the scrotum enlarges; investigation of its skin reveals the presence of dilated thick-walled lymphatic vessels that sometimes rupture. Lymph scrotum is frequently combined with an acute enlargement of the inguinal and femoral lymph nodes which may attain the size of a fist.

The abscesses caused by wuchereriosis are formed under the skin, in the muscles, thoracic and abdominal cavities, and genitalia. Spontaneous rupture of these abscesses may bring on grave complications—empyema, peritonitis, suppurative inflammation of the genitalia. Cases of filarial arthritis have been described.

The symptom most characteristic of tertiary or obstructive wuchereriosis is elephantiasis (Fig. 99). This condition commonly appears on the lower extremities, genitalia, discretely on the trunk, and very rarely on the face. On the lower extremities the elephantiasis may be either uni- or bilateral; it affects the leg below the knee, the foot, or the entire extremity.



Fig. 99. Elephantiasis caused by *W. bancrofti* (case reported by Kumbis)

In severe cases the limb may acquire gigantic dimensions, turning into a shapeless lump with thick transverse folds. Papillamatus and wart-like growths, eczema, and trophic ulcers appear on the skin; muscular atrophy develops. The patient becomes an invalid.

When the upper extremities are involved the elephantiasic process is more frequently seen in the wrist and forearm. The weight of an elephantiasic scrotum may reach 25 kg. In women the mammary glands turn into enormous tumour-like formations hanging down to the knees and lower. Elephantiasis of the female genitalia is manifested by enlargement of the vulva. In rare wuchereriosis cases edema and inflammation of the upper eyelid, and even its elephantiasis are observed.

Infestation with *W. malayi* causes elephantiasis only on the extremities, while *W. bancrofti* involves the genitalia as well. Complications due to secondary infections lead to elephantoid fever. In some instances a fever is the principal symptom of wuchereriosis. Eosinophilia is often observed.

## Diagnosis

Wuchereriosis is diagnosed on the basis of clinical and laboratory findings.

One of the characteristic symptoms of the helminthiasis is elephantiasis. However, it must be borne in mind that this condition may also be the result of thrombophlebitis, streptococcal infection of the lymphatics, and of other causes.

The decisive factor in diagnosis is the demonstration of the microfilariae in the blood. Blood specimens must be taken both during the day and at night, as the microfilariae of *W. bancrofti* and *W. malayi* concentrate in the peripheral blood vessels at night, of *W. pacifica* both day and night, and of *Loa loa* only during the day (see lower).

The simplest method of analysis is the examination of a fresh drop of blood under a cover-glass at low magnification; if present, the motile filariae are visible. Structural details are studied with an immersion lens.

Fixed preparations are made by placing a thick drop of blood on a slide glass (as for malaria parasites); the drop is dried in the air, then the erythrocytes are leached out with distilled water, the preparation is fixed in methanol or absolute ethyl alcohol and stained with the Romanovsky stain. Sometimes the number of microfilariae in the blood is so scanty that in order to demonstrate them it is necessary to employ the concentration method. For this 1 ml of venous blood is placed in 9 ml of a 2 per cent solution of formalin in distilled water. The mixture is centrifuged and the sediment is examined for the parasites. According to another method the blood is mixed with 5 per cent sodium citrate, the erythrocytes are hemolysed in distilled water, slightly acidified with acetic acid, and the mixture is centrifuged. The liquid over the sediment is decanted and replaced by water, and again centrifuged. This procedure is repeated until the liquid over the sediment becomes colourless. Concentration (or accumulation) methods are particularly valuable in elephantiasis, when it is very difficult to discover the microfilariae in the blood. Occasionally they are even absent from the blood at later stages of the disease as a result of the destruction of the adult wuchereriae or their isolation in the lymphatic system. In chyluria the microfilariae may be found in the urine. Immunological methods of diagnosis employed are the complement-fixation test, the precipitation reaction and the intracutaneous allergic test with an antigen from *Dirofilaria immitis* (canine filariae).

## Prognosis

Prognosis for wuchereriosis may be grave, as the disease, particularly in the presence of complications (peritonitis and others) and secondary infections, may result in complete invalidity or even death.

## Pathology and pathogenesis

In discussing the pathogenesis of wuchereriosis factors that should be taken into account are the mechanical effects of the worms, toxico-allergic reactions, and the possibility of the superimposition of a secondary bacillary infection.

The lumpy accumulations of wuchereriae in the lymphatics, including the thoracic duct, may partially or completely obstruct the lumens of these vessels and thus impede or cut off the flow of lymph. As a result the lymph nodes enlarge and varicose dilatations of the lymphatic vessels are formed. This, in its turn, is conducive to rupture of the lymphatic vessels of the kidneys, bladder, testis membranes, peritoneum, and intestines.

Necrotic sites are formed in the lymph nodes and vessels and adjacent tissues, accumulations of macrophages, giant and epithelioid cells are observed, and fibrosis with constriction and even closure of the lumens of vessels develop; occlusion of the latter may be due to the proliferation of their endothelium.

Filarial lymphangitis and lymphadenitis with protracted lymph stasis and transudation of the lymph with subsequent connective tissue proliferation terminate in elephantiasis of different parts of the body.

Changes in the intima of the lymph vessels caused by adult wuchereriae favour the development of staphylococcal and streptococcal infections. The sites of attachment of the helminths, particularly of dead ones, may give rise to the formation of abscesses as a result of a secondary infection, or even without it.

Sensitisation of the organism by the products of helminthic metabolism and the products of decomposition of the adult wuchereriae and microfilariae induce allergic reactions: eosinophilia in the tissues and the blood, skin eruptions.

## Treatment

Specific therapy for wuchereriosis is conducted with hetrazan (synonyms: banocide, notecin, caricide, carbylzan), the basic component of diethylcarbamazine citrate (I-diethylcarbamil-4-methylpiperazine dihydrogen citrate).

In the Soviet Union an analogous preparation is manufactured under the name of ditrazin. Hetrazan is particularly effective against the microfilariae, but it is also toxic for the adult wuchereriae; it evidently either kills or sterilises them, rendering the females incapable of producing larvae. For adults hetrazan is prescribed in peroral doses of 0.1 g 3 times a day on ten successive days; children are given single doses of 2 mg/kg. In the presence of microfilariae in the patient's blood a second course of treatment is prescribed several weeks later (Hawking, 1956). Possible side effects are loss of appetite, nausea, vomiting, headache, and insomnia. The destruction of the microfilariae and adult worms by drugs and the sensitisation of the organism by the products of their decomposition



frequently result in allergic reactions in the form of fevers, coughing, skin eruptions; these symptoms clear up in several days.

Rp. Ditradini 0.1  
D.t.d. No. 12 in tabul.  
S. 1 tablet three times a day

If an elephantoid fever and other symptoms of a secondary infection appear antibiotics are prescribed—penicillin, streptomycin, biomydin (aureomycin). A certain mitigation of the size of the enlarged parts of the body affected by elephantiasis is occasionally achieved with cortisone and ACTH. In involvement of the lower extremities an elastic bandage may prove beneficial. However, conservative treatment frequently does not achieve the desired results, and surgical intervention becomes necessary.

### Prophylaxis

Wuchereriosis is brought under control by extermination of mosquitoes with DDT preparations and other insecticides, by mass treatment of patients, and by chemoprophylaxis.

In heavy endemic sites of this helminthiasis hetrazan (detradin) is administered to the entire population without exception during the first year of the campaign against the disease; in the second year the drug is prescribed to prove carriers of the parasites.

### ONCHOCERCIASIS

Onchocerciasis is a worm disease the most characteristic features of which are lesions of the skin, subcutaneous connective tissue and eyes. There are two types of onchocerciasis, African and American, caused by species of the genus *Onchocerca* (Diesing, 1841) with closely allied biological and morphological features.

### Etiology

The African onchocerciasis is caused by the filarial worm *Onchocerca volvulus* (Leuckart, 1893). The white body of this parasite tapers slightly at both ends. The male is 30 mm long and 0.13 mm broad, the female reaches up to 500 mm in length and about 0.36 mm in breadth. The length and breadth of the microfilariae are respectively 0.3 and 0.008 mm. In the body of their definite host the adult worms encapsulate in peculiar tumours in the subcutaneous connective tissue.

American onchocerciasis is caused by *Onchocerca caecutiens* (Brumpt, 1919). The male of this filarial worm measures 24-42 mm in length and 0.154-0.19 mm in breadth; the female is 50 mm by 0.3 mm. The length of the microfilariae is 0.25 mm, their breadth is 0.008 to 0.01 mm. The adult parasites are located in nodules under the skin and under muscular aponeuroses or under the periosteum, predominantly on the head. The

definite host to both species of *Onchocerca* is man; the intermediaries and vectors of the disease are insects of the genus *Simulium*—*S. damnosum* and other species (buffalo gnats, turkey gnats, black flies or jinja-flies).

### **Epidemiology**

The source of infestation are people afflicted with onchocerciasis. In the human body the female worms give birth to their larvae, the microfilariae; the latter concentrate prevalently in the superficial layers of the skin, frequently in an eye, occasionally in the inguinal, femoral and cervical lymph nodes, in the viscera, and very rarely in the blood. The insect intermediary ingests the microfilariae with the blood extracted from its victim; from the insect's stomach the microfilariae migrate to the thoracic muscles where they develop within 6 days, occasionally longer, become infestive, and then migrate to the head and maxilla of the vector. When the insect attacks man the microfilariae break through the membrane of the maxilla, penetrate the human skin, then migrate into the lymphatic system and the subcutaneous connective tissue, where they attain sexual maturity.

### **Geographical distribution**

African onchocerciasis is widespread in Equatorial Africa: Sudan, Kenya, Uganda, Nyasaland, Angola, the Republic of Congo, Cameroon, Nigeria, Ruanda-Urundi, Ghana, Liberia, Gabun, Ubangi-Shari; it has been registered in Tunisia, Rhodesia, Tanganyika. Endemic sites of American onchocerciasis exist in Brazil, Mexico, Costa Rica, Venezuela, Guatemala.

### **Clinical aspects**

Symptoms most typical of onchocerciasis are firm, movable, often painful nodular subcutaneous formations, ranging in size from a pea to that of a pigeon's or even a hen's egg. These nodular tumours are located on the upper and lower extremities, mostly in the area of a joint, on the trunk and head (usually the occipital part), in the pelvis and the ileocecal area (Fig. 100).

Xerodermia (dryness and scaliness of the skin) is frequently observed. Occasionally fine papular eruptions appear, attended by pruritus, malaise, fever, headache. These papules may become the sites of blisters or pustules; when the latter rupture ulcers are formed in their stead, and scars remain after these ulcers have healed. In late stages of the disease spotty depigmentation of the skin occurs, mostly on the neck and back. American onchocerciasis is often attended by a dermatitis resembling erysipelas. The affected areas of skin become dark-red, edematous, the patient's temperature goes up to 39-40°, his ears and lips are swollen and deformed. In chronic relapsing cases the affected skin is hard, edematous, the ears are enlarged and curve forward. In some patients exacerbation of the

disease is observed every 2-3 weeks, the attacks lasting from several days to several weeks.

Cases have been described of onchocercial lymphadenitis, orchitis, hydrocele, elephantiasis of the scrotum and lower extremities, abscesses, arthritis, and wasting of the skull bones at the site of the filarial tumour, followed by attacks of epileptoid convulsions.



Fig. 100. Onchocerciasis caused by *O. volvulus* (case observed by Chesterman a. Manson-Bahr)

Various ocular complications follow the penetration of the microfilariae into the eye. In some patients the presence of the parasite in the conjunctiva does not provoke any marked clinical symptoms, while in others a chronic conjunctivitis develops, with hyperemia and thickening of the conjunctiva; occasionally reddish nodules with perimeters of about 2 mm are formed. The microfilariae concentrate more intensively, owing to phototropism, in the limbus (area of cornea-scleral junction); a conjunctival elevation in the form of a red rim 2-3 mm wide is then visible in this area.

The microfilariae also penetrate into the cornea, causing keratitis, photophobia, lacrimation and blepharospasm. At first only the peripheral areas of the cornea are involved, causing no noticeable disorders of vision; gradually the process spreads over the entire cornea, bringing on a stable opacity and pannus. Decomposition of the microfilariae in the orbit is followed by the appearance of a brownish exudate in the anterior chamber of the eye; this exudate presses on the retina and thus causes pupillary deformation. It is not uncommon for the retina to atrophy in onchocerciasis, losing its pigment. Onchocercial iridocyclitis may lead to the formation of a secondary cataract, to glaucoma and even atrophy of the eye. Chorioretinitis and atrophy of the optic nerve are occasionally observed.

## Diagnosis

It is not particularly difficult to diagnose onchocerciasis in a patient. The existence of the characteristic nodules and ocular lesions suggest this helminthiasis. The microfilariae are detectable in the eye by means of a corneal microscope and electric ophthalmoscope. The microfilariae may be found in thin layers of skin sliced off with a razor and placed on a slide in normal saline solution.

## Prognosis

Prognosis is grave, as ocular involvement may cause loss of sight.

## Pathology and pathogenesis

Both the adult *Onchocerca* worms and their microfilariae affect the human organism. The adult helminths are usually encapsulated in connective tissue nodules, but occasionally this does not occur and the parasites lie freely in the tissues. Infestation of the skin with microfilariae leads to a deterioration of the subepidermal and dermal elastic fibres, thickening of the epidermis, depigmentation of the skin. Upon invading the organ of vision the microfilariae cause inflammatory reactions, the appearance of small nodules in the conjunctiva, hemorrhages, atrophy of the optic nerve.

Sensitisation of the organism, eosinophilia, and other allergic symptoms occur in onchocerciasis, just as they occur in other helminthiases.

## Treatment

Therapy of onchocerciasis is associated with great difficulties. Hetrazan destroys the microfilariae, but the adult worms are only slightly susceptible to it. A more effective agent is antrypol (synonyms: suramin, Bayer 205, germanin, Fourneau 309, moranyl, naganol). This preparation kills only the adult worms, after which the microfilariae gradually disappear. A 10 per cent solution of antrypol is administered intravenously once a week, beginning with 0.5 g (5 ml of the solution) and gradually bringing the dose up to 1 g (10 ml of the solution). The duration of treatment is 5 to 10 weeks. Side effects usually appear in the fifth week of treatment, expressed by arthritic pains, fever, pruritic erythematous skin eruptions, transient conjunctivitis and photophobia.

The microfilariae are rapidly killed off with hetrazan. It should, however, be remembered that intensive decomposition of the worms often evokes allergic reactions that may be quite severe and lead to exacerbation of the ocular lesion. Therefore, treatment should be carried out in hospital conditions under the observation of an eye specialist, and the drug must be given in gradually increasing doses. Hawking (1956) recommends 0.025 g of the preparation on the first day of treatment, and two 0.025 g

doses on the second day. If the reaction to the substance is not great the patient is given a full daily dose of 0.1 g three times a day for ten consecutive days. The most expedient procedure is to combine hetrazan per os with intravenous injections of antrypol. Manson-Bahr (1954) recommends combined treatment with both preparations, Hawking (1954) prefers prescribing hetrazan first and antrypol later. Desensitisation with cortisone and ACTH may prove beneficial in the prevention of allergic reactions.

The onchocercomas (the onchocercial tumours) are removed surgically.

### **Prophylaxis**

Onchocerciasis is combated by treating patients and parasite carriers, by destroying the jinja-flies, gnats and other vectors and their larvae in flowing streams of water, and by individual protection against insect bites. It is recommended to take hetrazan every six months for checking the infection before the onset of clinical symptoms.

### **LOAIASIS**

Loaiasis is a filariasis the most outstanding features of which are Calabar swellings—edematous areas on various parts of the body, predominantly the extremities.

### **Etiology**

The parasite causing this disease is *Loa loa* (Guyot, 1778), a white semi-transparent filarial worm. The male measures 30 to 34 mm in length and 0.35 to 0.43 mm in breadth; the female is 50-70 mm by 0.5 mm. The length of the microfilariae is 0.30 mm and their breadth 0.006-0.008 mm. Man and probably some primates are the definite hosts. The adult worms live in the subcutaneous tissues, under the conjunctiva of the eye and under serous membranes, including the pericardium. The microfilariae infest the blood, occasionally the cerebrospinal fluid. The intermediate hosts and vectors of the disease are various "mangrove flies"—*Chrysops dimidiata*, *Ch. silacea* and other *Chrysops* species of tabanid biting flies.

### **Epidemiology**

The source of infestation are humans afflicted with loaiasis, and evidently also infested monkeys. During the day the microfilariae of this parasite accumulate in the peripheral blood, therefore being called *Microfilaria diurna*. When the chrysops feed on the blood of infested people they ingest the microfilariae; the further development of the parasites occurs in the connective tissue of the abdomen and thorax of the insect. They become infestive within 7 to 10 days and migrate to the insect's head. When the fly feeds the microfilariae emerge and are deposited on the surface of the human skin which they very rapidly burrow into. The *Loa loa* worms attain their adult stage in 6 to 18 months.

## Geographical distribution

Loiasis has been registered in the following countries of Africa: North Rhodesia, Angola, the Republic of Congo, Ruanda-Urundi, Cameroon, Liberia, Ghana.

## Clinical aspects

Occasionally infestation may evoke no noticeable clinical symptoms, while in other cases it causes marked disorders.

Soon after infestation many patients experience a slight fever, pain in the extremities, paresthesia, urticaria. At later stages the migration of the adult worms under the skin causes pruritus and burning sensations; their penetration of the eye is attended by edema and hyperemia of the conjunctiva, swelling of the eyelids, not infrequently by insufferable pain; migration of the parasites to the urethra causes pain, particularly during urination.

In many patients the skin on limited areas of the extremities, face, and other parts of the body periodically becomes edematous and pallid, or, on the contrary, red and hot to touch. The edematous areas are not tender, no pitting is noted. The appearance of these swellings is spontaneous, but they resolve very slowly, usually in days or even weeks. Occasionally a hydrocele may be formed.

Abscesses in the muscles and in the axillary and inguinal lymph nodes have been reported to result from the destruction of the adult worms and a secondary infection. Schofield (1955) holds that the allergic reactions that bring about the destruction or encystment of the helminths near nerve stems may be the cause of neuritis.

Kivits (1952) has suggested that by penetrating between the cerebral meninges the microfilariae are capable of causing encephalitis. Usual blood findings in loiasis are eosinophilia, in some patients as high as 80 per cent, and secondary anemia.

## Diagnosis

In hot climates the finding of a Calabar swelling in a patient should always suggest loiasis, and the parasite should be looked for in the blood.

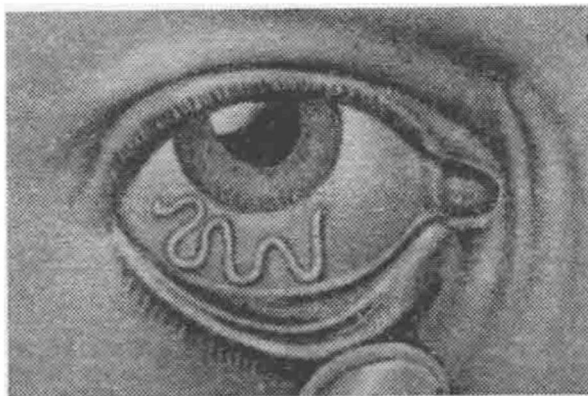


Fig. 101. *Loa loa* in the conjunctiva (Fulleborne)

The worms are quite discernible to the naked eye under the conjunctiva (Fig. 101). Specific immunological tests are likewise employed for diagnosing the helminths—the complement-fixation test and the intracutaneous allergic test.

### Prognosis

Prognosis for life is favourable. No authentic cases of death due to loaiasis have been reported; however, the disease may run a very protracted course with periodic exacerbations.

### Pathogenesis

The leading factor in the pathogenesis of loaiasis is sensitisation of the organism by the waste and metabolic products of the worms, which induces a number of allergic symptoms including the Calabar swelling that is very like Quincke's disease (angioneurotic edema). The mechanical irritation and trauma of the tissues caused by the worms as they migrate in the tissues of their host, often with a speed of over 1 cm per minute, are also important. Secondary infections lead to the formation of abscesses.

### Treatment

The most effective drug is hetrazan, given perorally in daily doses of 0.4 g to adult male and 0.3 g to adult female patients for a period of 10 to 20 days. Frequent allergic reactions to therapy are pruritus, erythema, Calabar swellings; these symptoms are alleviated or even eliminated by the administration of dimedrol (synonym: benadryl hydrochloride, the antihistaminic substance diphenhydramine hydrochloride). This substance is given by mouth in 0.05-0.1 g doses once or twice a day, or intramuscularly in a 1-2 per cent solution, 0.02-0.05 g of the preparation per injection.

### Prophylaxis

Loaiasis is combated by the treatment of patients and the extermination of the fly vectors.

### ACANTHOCHEILONEMIASIS

Definition: a morbid condition caused by a parasitic worm that infests the cavities of the body.

### Etiology

The pathogenic organism is *Acanthocheilonema perstans* (Manson, 1891). Synonym: *Dipetalonema perstans*.

The worm is white and transparent. Its anterior end is rounded, the tail end carries two appendages. The male measures 40 to 45 mm in length by 0.06 to 0.08 mm in breadth, the female 70-80 mm by 0.12-0.14 mm.

The microfilariae exist in two forms—long and short. The first are 0.16-0.2 mm by 0.005-0.006 mm, the second 0.09-0.11 mm by 0.004 mm. Man is the definite host; the adult worms live in the peritoneum, the pararenal and retroperitoneal tissues, and in the pericardium, while the microfilariae infest the blood. The intermediate hosts are the bloodsucking midges *Culicoides austeni*, *C. grahami*, and others.

## **Epidemiology**

The disease is transmitted from infected to healthy people by *Culicoides* midges that ingest the microfilariae with the blood of their victims. Within 7 to 10 days the larvae become infestive and migrate to the proboscis of the insect, from whence they emerge onto the human skin and penetrate it.

## **Geographical distribution**

Endemic sites of acanthocheilonemiasis have been registered in a number of African countries. Sporadic cases have been reported from Argentina.

## **Clinical aspects**

The clinical features of this disease have been studied very scantily. Strohschneider (1956) reports that patients complain of dizziness, pain in the extremities, chest and abdomen, periodic pruritus. Medical examination shows a slight enlargement of the liver and spleen, occasionally febrile paroxysms accompanied by an urticarial rash. In severe forms edematous areas resembling Calabar swellings appear on the extremities, scrotum, and penis.

## **Pathogenesis**

The pathogenesis of this disease is not at all clear. The leading factor is probably systemic sensitisation with subsequent allergic reactions.

## **Treatment**

The preparation prescribed for treatment is hetrazan, but it destroys only the microfilariae, therefore only temporary clinical and parasitologic effects are obtained. The microfilariae disappear from the blood, but within one week to three months after termination of treatment a new generation appears. Hetrazan is prescribed perorally for ten consecutive days in daily doses reaching 0.5 g. Upon intensification of allergic symptoms the patient is given dimedrol (benadryl hydrochloride) or ACTH.

## **Prophylaxis**

Acanthocheilonemiasis is combated by extermination of midges and protection against their bites.

## **DIROFILARIOSES**

In man three parasitic species of the genus *Dirofilaria* (Railliet a. Henri, 1911) have been registered: *D. magalhaesi* (Blanchard, 1896), *D. louisianensis* (Faust, Thomas, a. Jones, 1941), *D. repens* (Railliet a. Henri, 1911).



*D. magalhaesi* was discovered in the hearts of two people, the first an inhabitant of Rio de Janeiro, the second of New Orleans. The male is 83 mm in length and 0.28-0.5 mm in breadth, the female is 155 mm by 0.6-0.8 mm. The second species (*D. louisianensis*) was found in the heart of a woman in New Orleans. The length of the male was 120 mm, its breadth 0.52 mm.

*D. repens* (an adult male) was extracted from a subcutaneous node in the lower eyelid (K. I. Scryabin et al., 1929). A number of cases of encapsulation of the immature helminths of this species have been described in various countries.

### MANSONELLIASIS

Synonym: Filariasis Ozzardi.

The pathogenic agent of this disease is *Mansonella ozzardi* (Manson, 1897). The male is known only by the tail end of its body, 32 mm in length and 0.2 mm in breadth, while the female is 65 mm long and 0.21-0.5 mm broad. The microfilariae measure 0.173-0.240 mm by 0.004-0.005 mm.

The definite host is man, in whom the adult filarial worms live in the peritoneum and under the serous membrane of the peritoneal cavity, while the microfilariae circulate in the peripheral blood. The intermediate hosts are *Culicoides* midges and *Aedes aegypti* and *Anopheles maculipennis* mosquitoes.

Mansonelliasis is widespread among the population of South America and the West Indies. Its vectors are mosquitoes, the intermediate hosts.

Montestruc (1949) considers that these worms cause the formation of an adeno-lymphocele.

*Prophylaxis* is the same as for other filarial worm diseases.

*Treatment* is performed with hetrazan.

# STRONGYLOIDIASIS

---

Strongyloidiasis (anguilluliasis) is a worm disease the early stages of which are marked by a predominance of allergic skin and lung symptoms; in later phases gastrointestinal disorders prevail.

Strongyloidiasis was first described by Normand in 1876 under the term "Cochin-China diarrhea". The basic life-history of the parasite was worked out by Leuckart in 1882.

## ETIOLOGY

Strongyloidiasis is caused by the round worm *Strongyloides stercoralis* (Bavay, 1877). Synonym: *Anguillula stercoralis* (Bavay, 1877).

The male of the parasitic generation is 0.7 mm long and 0.04-0.06 mm broad. Its ventrally curved tail-end carries two spicules and a gubernaculum. The female worm measures 2.2 by 0.03-0.07 mm. The elongated ova are transparent; they measure 0.05-0.058 by 0.030-0.034 mm.

In its metamorphosis this parasite goes through alternating generations of free-living and parasitic forms. In the human body the adult females of the parasitic generation infest the internal layers of the mucous membranes, chiefly the Lieberkühn glands of the duodenum; in very heavy infections they invade the mucous membrane of the pyloric portion of the stomach, the entire small intestine, cecum and colon transversum, and even the biliary and pancreatic ducts.

The fertilised females deposit their ova, from which rhabditoid larvae emerge into the intestinal lumen; these larvae possess a double-bulbed esophagus. They measure 0.2-0.3 by 0.014-0.016 mm, and are voided in the feces of the host. In the outer environment two types of development are possible. If conditions are unfavourable the rhabditoid larvae turn into filarial larvae possessing a cylindric esophagus; in favourable conditions they develop into free-living males and females. After copulation the females deposit eggs from which a second generation of rhabditiform lar-

vae are hatched. These larvae develop either into a new generation of free-living worms, or turn into filarial larvae. The filarial larvae are infestive; they penetrate into the human body through the skin or by the mouth with food and drink. In both cases they go through a migratory stage in the host's body, passing through the lungs to the pharynx, from whence they are again delivered to the stomach and thus finally penetrate into the intestine. During this migration the worms attain sexual maturity. The females are fertilised in the lungs or the intestinal lumen; after copulation the males perish.

### EPIDEMIOLOGY

The source of infection are human hosts of *Strongyloides* worms. Infection is contracted by contact with soil containing the infestive larvae of the strongyloids, and by drinking water or eating food contaminated with the larvae. Conditions for the preservation and development of the worms in the outer environment are particularly favourable in warm humid climates, as well as in moist mines and tunnels where the temperature is high. This is why strongyloidiasis is mostly encountered among the population of certain tropical and subtropical countries and among miners. Naturally, the rate of infestation also depends on the sanitation in populated communities and mining enterprises.

### GEOGRAPHICAL DISTRIBUTION

Strongyloidiasis is for the most part a disease of the tropics and subtropics. In Brazil, for instance, it is diagnosed in 12-35 per cent of people subjected to examination, in Panama in 18-31 per cent, in Vietnam in 18 per cent, in Japan in 12 per cent. Sporadic cases are encountered in lands with temperate zones.

### CLINICAL ASPECTS

The early migratory phase of strongyloidiasis is marked by fever, pruritus, urticaria or papular eruptions and local edema; eosinophil infiltrations are noted in the lungs. Occasionally the infestation may be devoid of any clinical symptoms, or these symptoms may be so slight as to attract no attention.

In late phases of the disease, when the worms have attained sexual maturity, some individuals may remain simple carriers, others may have the disease in a mild form, but there are also quite a few markedly affected patients, and even severe cases with lethal termination. The latter have been reported only from the tropics and subtropics.

In mild cases of strongyloidiasis the patients complain of nausea and a dull pain in the epigastric region. The stools are either normal or mushy, 1-2 times a day; occasionally constipation alternating with light diarrhea is observed.

In frank forms the nausea is frequently accompanied by vomiting and acute pains in the epigastric region that usually appear on an empty sto-

mach or 2-2 $\frac{1}{2}$  hours after meals, occasionally during the night. Some patients complain of pains in the right or left subcostal areas, in the iliac region or the entire abdomen. Attacks of severe pain in the right subcostal and epigastric regions are not uncommon, and they are accompanied by fever and urticarial eruptions. Diarrhea appears periodically (5-6 times in 24 hours). The stool is watery, at times with admixtures of mucus, less frequently — blood. Cytological examination of the feces demonstrates numerous muscular fibres and leukocytes. In some cases the liver is enlarged and hard, the sclera subicteric. Blood counts reveal eosinophilia (up to 70-80 per cent) in the majority of patients; in protracted cases secondary anemia appears, usually moderately expressed. Lowered gastric acidity is observed, less frequently the acidity is increased. The duodenal juice contains the larvae of the strongyloid worms, an increased amount of mucus, leukocytes and epithelial cells. Radiography reveals symptoms of dyskinesia of the duodenum — duodenostasis. Nervous system symptoms are headache, dizziness, increased mental fatigability, neurasthenic and psychosthenic signs.

In severe cases of strongyloidiasis the diarrhea becomes continuous, the fetid stools contain many particles of undigested food, mucus, and blood. Dehydration of the organism occurs, a severe secondary anemia and cachexia develop. Some authors describe hypochromic anemia of a pernicious type as attending strongyloidiasis, but the present authors think that these cases were probably a combination of helminthiasis with sprue or the Addison-Biermer disease (pernicious anemia).

Intraintestinal autoinfestation accompanied by the migration of filariform larvae to the portal vein and pulmonary circulation may cause bronchopneumonia and eosinophil infiltration of the lungs with ejection of sputum containing great numbers of the parasites. Such cases have been described by A. A. Laptev (1945), V. P. Podyapolskaya (1950), R. V. Glusker and I. I. Gromova (1956), and other authors.

An analysis of the clinical features of strongyloidiasis shows that its early stages are characterised by allergic reactions of the skin and lungs, while in late phases the predominant symptoms are duodenitis, enterocolitis, dyskinesia of the biliary tract, less frequently angiocholitis and hepatitis.

## DIAGNOSIS

Strongyloidiasis is diagnosed by the demonstration of the parasitic larvae in the duodenal juice, feces and sputum. The ova are passed in the stool very rarely, and then only in cases of severe diarrhea. The duodenal juice is obtained by the ordinary intubation procedure; the specimen is centrifuged and the sediment is examined under the microscope. The greatest number of larvae is contained in portion A. The methods evolved by Schulman and Baermann are employed for finding the strongyloid larvae in fecal matter.

The Schulman method: 2-3 g of feces are emulsified in a three- to five-fold volume of boiled or distilled water or of normal saline solution. The

emulsion is stirred with a rotary movement by means of a glass rod. The larvae and ova concentrate in the centre of the liquid around the rod; the latter is quickly withdrawn and the drop that falls from it is placed on a slide and examined under the microscope.

**The Baermann method:** this method calls for the use of a glass funnel to which a rubber tube with a clamp is attached. Water warmed to 50 °C is poured into the funnel through a metal sieve containing 5 g of feces, the sieve is placed over the funnel so that the lower portion of the feces is immersed in water. The strongyloid larvae actively emerge into the warm water and concentrate in the rubber tube above the clamp. Two to four hours later the clamp is loosened and the liquid let out into centrifuge tubes; after 1-2 minutes of centrifugation the sediment is examined under the microscope.

The sputum may be examined in native smears, but it is better to place it in a small flask with an equal volume of 0.5 per cent sodium or potassium hydroxide, then shake it well for 5 minutes, warm up slightly in a water bath and examine the sediment after centrifugation. In order to demonstrate living larvae a 24-hour specimen of sputum is processed by the Baermann method. All patients with a high eosinophil count in the peripheral blood should be examined for strongyloidiasis.

### **PROGNOSIS**

Favourable for temperate climates, it is occasionally grave in sub-tropical and tropical zones.

### **PATHOLOGY AND PATHOGENESIS**

Infestation of the intestine by the female strongyloids and their larvae cause catarrhal inflammation, swelling of the follicles, and occasionally erosions. Vesicles appear in the depth of the mucous membrane, and small granulomas, consisting of histiocytes, a small number of giant cells, plasmacytes and numerous eosinophils, are formed. The penetration of the larvae into the lymphatics of the submucosa leads to the development of granulomatous endolymphangitis. The granulomatous inflammation causes some larvae to encapsulate. The larvae that penetrate into the mesenteric lymph nodes are surrounded by eosinophils. R. V. Glusker and I.I. Gromova (1956) observed an ulcerative lesion of the ileum.

The pathogenic effect of the helminths is due to the sensitisation produced by their metabolic and waste products, and to tissue injury. Lesions of the barrier of the intestinal wall, particularly in the presence of erosions on the mucosa, are conducive to the penetration of bacteria. It is also quite probable that the larvae and adult parasites discharge cell-dissolving substances.

Another factor that must be taken into consideration is intrainestinal autoinfestation that may sometimes occur, particularly in cases of constipation (K. I. Scryabin and G. F. Wagner, 1924, and other authors). In

such cases the rhabditiform larvae develop into filarial larvae in the patient's intestine. These larvae migrate in the body of the host, finally turning into adult forms, and the females penetrate into the intestinal mucosa. Owing to repeated intrainestinal infestation the number of parasites increases and their pathogenic effect grows. In the process of their migration part of the larvae penetrate into the systemic circulation and are conveyed to various organs. Faust (1932) holds that they are capable of penetrating into any organ or cavity of the human body.

### **TREATMENT**

The agents employed for strongyloidiasis therapy are dithiazanine and gentian violet; the first is more effective.

Dithiazanine iodide (commercially produced under the trade-marks of "Telmid" and "Delvex") is prescribed for adults in doses of 0.2 g 2-3 times a day; children are given 10-20 mg/kg daily. One course of treatment continues for 5 to 21 days, until the larvae are no longer demonstrable in the feces and duodenal juice of the patient. The adult dose of gentian violet is usually 0.08-0.1 g in capsules per os 3 times a day, one hour before meals; the single dose for children is 0.005 g, the daily dose 0.01 g per year of life. Peroral administration may be alternated once or twice a week with duodenal intubation of 0.1 g of the preparation in 10 ml of water. The duration of treatment is 15 days; a second 7- to 10-day course is administered 1½ months after the first. In some cases the ingestion of gentian violet causes a loss of appetite, nausea, less commonly vomiting, abdominal pains. In such an event the medicine is given after meals instead of before, or treatment is discontinued for several days.

Rp. Gentian violeti 0.08  
Sacchari 0.2  
D.t.d. No. 12 in caps.  
S. 1 capsule 3 times a day

### **PROPHYLAXIS**

The prophylaxis of strongyloidiasis is the same as for ancylostomiasis.

# DRACUNCULOSIS

---

Synonyms: Dracontiasis, dracunculiasis, guinea worm.

This helminthic disease is caused by *Dracunculus medinensis* (L., 1758, *Filaria medinensis* (L.), (Gmelin, 1790); *Filaria aephiopica* (Valenciennes, 1856); *Gordius medinensis* (L., 1758); *Vena medinensis* (L., 1758), Gallandant, 1773); *Dracunculus graecorum* (Grüner, 1777); *Dracunculus aephiopicus* (Val.) (Scheidemühl, 1896); *Vermiculus capsularis* (Dunglison, 1895); *Dracunculus persarum* (Kaempfer, 1712); *Füllebornius medinensis* (L.) (Leiper, 1926).

In Central Asia and Iran both the disease and the parasite are called “rishta”, meaning thread, cord, string. In India the disease is called “noru” or “nikhrivo”, in New Guinea “irkon”, in the Arabian countries “irkalhibli” (threadlike vein). The physicians of Ancient Greece called the parasite “small dragon”, hence the name of the disease “dragontiasis”. Avicenna (Abu Ali ibn Sina) termed the parasite “irk-al-medini”, meaning Medina vein or worm. Even now the worm and the disease are known in some localities as medina worm, guinea worm, serpent.

## HISTORICAL DATA

Dracunculosis is one of the most ancient of parasitic diseases of mankind. In accordance with the hypothesis of L. M. Isayev (1930) it first appeared in Africa as a natural endemic disease of wild animals—tigers, monkeys, apes, baboons, etc., which inhabited the jungles near small lakes. From Africa the disease spread to other continents.

In the medical literature of Central Asia the first comprehensive description of dracunculosis was made by Abu Ali ibn Sina (Avicenna).

Of subsequent Central Asian authors Bakha ud-Davla is quite noteworthy. In his treatise *Hulosat-ut-tajarib* (*Essence of Experiments*) (1501) he described the clinical features of the disease and also pointed out the importance of water in its diffusion.

The Uzbek physician Mahmud Hakim Mohammed Yaipani (end of the 19-th century) wrote that the parasite develops from tiny germs inhabiting stagnant water.

A circumstantial description of dracunculosis in the khanate of Bukhara was made by the Russian traveller N. V. Khanykov who visited Bukhara as a member of an expedition headed by L. F. Butenev.

Khanykov quotes local inhabitants as saying that the parasite develops from germs in the stagnant waters of the "khausas" (cisterns or stepwells in towns). He describes the methods employed by the "tabibs" (local physicians) for curing rishta, and also dwells on the multiple infestation of man by this worm.

## ETIOLOGY

*Dracunculus medinensis* (L., 1758) belongs to the phylum *Nemathelminthes*, class *Nematoda*, family *Dracunculidae*, genus *Dracunculus*.

The female parasite is 30 to 120 cm in length and 0.5-1.7 mm in breadth. There is a cuticular cap or shield on its anterior end, the mouth is surrounded by four double papillae. There are two ovaries, one in the anterior, the other in the posterior part of the body. The ovaries are contiguous with an uterus that almost entirely occupies the interior part of the body. The vulva is closed, therefore the larvae emerge through a rupture in the cuticle near the head, or through the mouth into which the contents of the uterus are emptied when the latter bursts after the head of the parasite has contacted water.

The dimensions of the larvae are 0.5-0.75 by 0.015-0.025 mm. The male worm is 12-29 mm by 0.4 mm. Its mouth surrounded by a ring of internal papillae carries two spicules, four pairs of pre-anal and six pairs of post-anal papillae.

The definite hosts of the dracunculus are man and less frequently dogs and monkeys. The intermediate hosts (vectors) are cyclops: *Cyclops coronatus*, *C. bicuspidatus*, *C. quadricornis*, *C. orthonoides*, *C. vicinus*, *C. uljanini*, *Macrocyclus fuscus*, *Eucyclops serratulus*, etc.

Basic contributions have been made in the study of the problem of dracunculosis by Russian scientists.

The prominent Russian biologist and traveller A. P. Fedchenko studied rishta (dracunculosis) in Uzbekistan in 1869 and discovered the cyclop vector of the disease; however, Fedchenko held that infestation of the cyclops occurred by active penetration of the microfilariae through their abdominal membranes. L. M. Isayev (1922) proved that the penetration of the microfilariae into the cyclops was due to their active ingestion by the latter (Fig. 103).

*Dracunculus medinensis* is a viviparous parasite. The number of larvae brought forth by the female reaches 8 to 10 million.

When the gravid female becomes ripe for bringing forth its larvae its head approaches the skin and a small papular induration is formed. Within several days this induration turns into a blister with a base up to 7 cm in diameter; the blister breaks open near its centre. When the area of the



body on which such a ruptured blister sits comes into contact with water, the water wets the uterus of the worm; the uterus ruptures, shedding forth a prodigious number of larvae. The latter swim out into the water where they are swallowed by cyclops. In the bodies of the latter the larvae undergo metamorphosis, moulting and becoming immobile. The definite hosts (man, dogs) become infected by ingesting the infested cyclops with raw water.

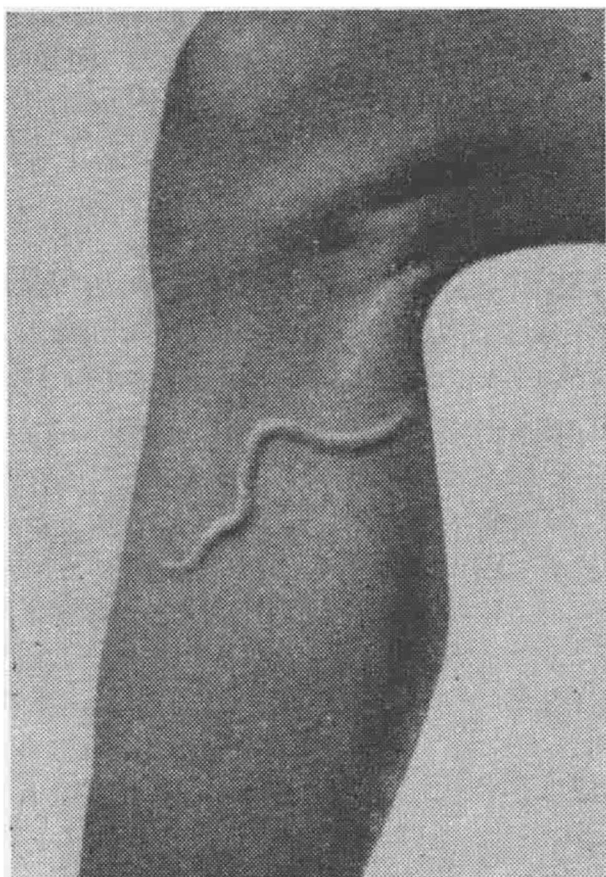


Fig. 102. *Dracunculus medinensis* in the subcutaneous tissue, skin intact. The worm is clearly outlined (L. M. Isayev)

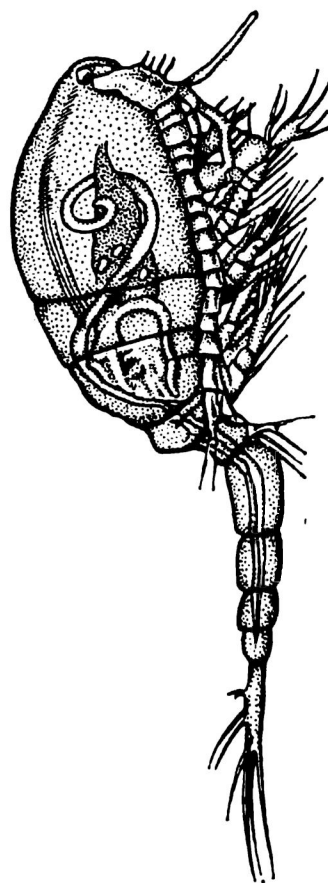


Fig. 103. Cyclops devouring the larva of a guinea worm. The cyclop has captured the worm, but has not swallowed it yet (L. M. Isayev)

The females mature in the human body within a period of 9 to 14 months. The adult dracunculus usually inhabits the subcutaneous tissues, less frequently deeper layers—the intermuscular connective tissue.

The favourite site of lesion are the lower extremities, although the parasite may localise in any part of the subcutaneous tissue. There is usually only one parasitic dracunculus present, less commonly several, in various parts of the body. Exceptional cases have been described when 17 to 50 parasites have been found in one patient.

#### GEOGRAPHICAL DISTRIBUTION AND EPIDEMIOLOGY

Dracunculosis is one of the most widespread of worm diseases. According to Stoll there were over 45 million dracunculosis patients all over the world in 1947, of them 15 million in Africa, 30 million in Asia, and about 100,000 in South America.

In Africa the disease is diffused over a large area. The endemic zone is located between the equator and the northern tropic; the incidence of guinea worm is particularly high among the population of Mauritania, Gabun, Senegal, Togoland, Dahomey, Nigeria, Cameroon. The vicinity of Lake Chad is also an endemic site of dracunculosis. Further the borderline of the disease runs to Sudan, Uganda and the valley of the Nile. A high dracunculosis rate is reported from Iraq (Medina worm), Saudi Arabia, Iran.

The western part of India is an enormous endemic area of dracunculosis. It has spread here to the regions east of Delhi and to separate central provinces of India. Moreover, dracunculosis is frequently observed in New Guinea and the West Indies, while in South America it is encountered chiefly in Brazil and Guiana.

On the territory of Central Asia (Turkestan) dracunculosis was formerly widespread in Old Merv (Mari), Karshi, Jizak, and Bukhara. It is a historical fact that dracunculosis disappeared from Old Merv as the result of the total annihilation of the population and the demolishment of the city by the hordes of Genghis Khan when they invaded Central Asia. This disease disappeared from Jizak when all the khausas (step-wells) in the city dried up in the 1890's owing to the destruction of the Iski-Tuyatar-tar canal that supplied the city with water. In Karshi dracunculosis disappeared during the Civil War after the inhabitants had abandoned the town and all the step-wells had dried up. A heavy site of dracunculosis remained in Bukhara alone, and in a number of communities around this city (over 10,000 patients).

Human infestation took place in the khausas contaminated by dracunculus-infested cyclops.

In Bukhara the spread of the infection was due to the following epidemiological factors: 1) bathing in the step-wells—contamination of the water by infected people; 2) ritual washing performed by the Moslem inhabitants in the aryks (ditches) that ran into the step-wells, and in the wells themselves, too; 3) water delivered by water-carriers (mashkobs) who stood on the well-steps with their bare feet to fill their vessels with water; 4) drinking raw infested water directly from the step-wells; 5) ingestion of infested cyclops when bathing; 6) drinking water vended by the water-carriers.

L. M. Isayev, who headed the Tropical Institute in Bukhara in the early 1920's, set himself the goal of eradicating dracunculosis from Bukhara and the nearby villages from where it could spread to other regions. Liquidation of dracunculosis in Bukhara and its vicinities meant liquidation of the disease throughout the U.S.S.R., in so far as Bukhara was the sole site of this disease in our country.

In his public statements made in Tashkent in 1923 Isayev emphasised that dracunculosis should be combated in two directions: first, timely diagnosis of the condition, registration of patients and enaction of measures for rendering them harmless (injection of drugs into the body of the parasite to destroy the embryos), and second, extermination of the cyclop intermediaries in the step-wells.

Isayev introduced a number of vigorous measures for the eradication of guinea worm infection, a task that was planned for a period of several years. The step-wells were cleansed and partially filled up with earth; absolutely all patients and mashkobs (water-carriers) were registered and kept under medical observation; sanitary instruction was carried out on a wide scale. One particular measure was that all patients, and the population at large, were advised to periodically pour the water residue out of the khoobs (vessels) in which it was kept and to cleanse the latter thoroughly. As a result of all these measures dracunculosis was liquidated in Bukhara by 1928, and after the construction of the city water mains in 1930 the danger of a recurrence of the disease in this city disappeared.

### CLINICAL ASPECTS

From the moment of infestation (ingestion of the larvae) until complete maturity of the females 9 to 14 months go by. The incubation period is asymptomatic. The prodromal symptoms appearing several hours before the development of a local necrotic site adjacent to the head of the parasite are evidently the result of absorption of toxic excretions of the mature parasite, and to allergic reactions of the organism. These prodromal symptoms are erythema or urticarial rash all over the body, pruritus, weakness. Possible subsequent symptoms are asthma, dyspnea, dizziness, nausea, vomiting and even diarrhea. As soon as the blister ruptures the above symptoms rapidly subside and gradually disappear altogether. The whitish necrotic mass surrounding the head of the parasite sloughs off in 7 to 10 days. An opening is visible in the centre of the base of the ruptured blister; this opening leads to the passage burrowed by the female worm, from which the latter's head protrudes. When the parasite is withdrawn completely (this calls for experience and skill) and no secondary infection has entered the wound, healing is quite rapid. Dirt infects the wound (this occurred as a rule in the past among the native population who were treated by illiterate medicine men and witch doctors) and the infection penetrates into the depth of the tissues along the track of the worm, and various complications—abscesses, phlegmons, arthritis, synovitis, and orchitis—appear.

In some cases the body of the parasite is outlined under the skin (Fig. 102), but in the majority of cases the worm is invisible until the blister ruptures. Occasionally it perishes before perforating the skin of its host and then undergoes petrification. In these cases the parasite is easily demonstrated by skiagraphy. Skin tests with extracts of the parasites yield no positive results. Eosinophilia is sometimes observed in the blood during the allergic or subsequent periods when the number of infestive parasites is great.

### TREATMENT

Dimedrol (benadryl hydrochloride), ephedrine, injections of adrenalin and calcium preparations are recommended for treating the toxico-allergic symptoms developing in the prodromal period.

Three methods are recommended for removing the parasite: 1) surgical removal through a wide incision in the skin; 2) injection of various toxic drugs into the tissue surrounding the worm and directly into its body; 3) gradual withdrawal of the worm by winding it on a roll of gauze or a wooden peg.

Surgical removal has been almost completely abandoned as it requires a large incision and the worm has to be drawn out by reeling anyhow. The numerous agents that have been proposed for infiltration into the tissues surrounding the worm are of no avail (emetine, corrosive sublimate, stibium [antimony] preparations, etc.).



Fig. 104. Withdrawal of the parasite from the wound in dracunculosis.

The *Manual of Tropical Medicine* by Mackie, Hunter, and Worth (1955) cites reports on satisfactory results obtained with injections of an emulsion of phenothiazine (a derivative of methylene blue). The emulsion is prepared by triturating 2 g of phenothiazine with 0.35 g of lanolin in a sterile mortar with 15 ml of sterilised olive oil (heated to 100°C for one hour). The addition of 5 ml of sterile water produces an emulsion to which another 20 ml of sterile olive oil is added, after which the emulsion is poured into a sterilised small bottle, sealed and autoclaved at 115°C for 30 minutes.

Two ml of 3 per cent novocain are injected into the vastus medialis muscle, slightly lateral to its centre, into the upper third of the gastrocnemius, and the dorsum of the foot. The well-shaken emulsion is injected into the same sites (20 ml, 10 ml, and 10 ml respectively). Injections are followed by vigorous massage for 5 minutes.

Contraindications for phenothiazine treatment are severe diseases of the heart and kidneys, epithelial hepatitis, and age less than 2-3 years.

The most effective method of removal is the one commonly adopted by the local population (on condition of aseptic management). First the uterus of the worm is emptied by forced parturition (wet pads and douche),

then the protruding head of the worm is grasped and very cautiously pulled out as far as it goes freely; this part is wound on a roll of sterile gauze or a thin wooden spool or peg, and the wound is bound up. Next day the parasite is again pulled out a little and the drawn-out part is again rolled on the gauze or peg. This procedure is continued day after day until the parasite comes out completely (Fig. 104).

# LAGOCHILASCARIDOSIS

---

Lagochilascaridosis is a morbid condition caused by the nematode worm *Lagochilascaris minor* (Leiper, 1909) which belongs to the family *Ascaridae* (Baird, 1853). The cuticula of this helminth is finely marked transversely. Lateral alae stretch along the entire length of its body.

The male measures 9 mm in length and 0.4 mm in breadth; the female is 15 mm by 0.5 mm. The eggs are round, with a thick, coarse shell and an 0.065-mm diameter. The worm usually infests the intestines of wild cats and leopards in South America. It has been found several times in man in Guiana and on the island of Trinidad. In these cases the parasites were located in subcutaneous abscesses, on the neck and in the corners of the jaw-bones, in the eye, in tonsillar abscesses, and in abscesses in the mastoid process. The worm load may be a very heavy one. Thus, Winkel and Treurniett (1956) removed hundreds of these worms from the abscesses of a Negro patient. Infestation is evidently acquired by ingestion of the ripe eggs. The larvae hatch in the intestine and then migrate all over the body with the blood stream.

Therapy is effected surgically by opening the abscesses and removing the worms. Hetrazan (ditrazin) was ineffective.

## HEPATICOLOSIS

---

Hepaticolosis is a disease of the liver caused by the nematode worm *Hepaticola hepatica* (Bancroft, 1893), a member of the family *Trichocephalidae*. Its synonyms are *Capillaria hepatica* and *Trichocephalus hepaticus*. The males and females are of the same size, 4-12 cm in length and 0.1-0.12 mm in breadth. The eggs resemble those of *Trichuris* worms, differing only by the presence on their shells of numerous tiny depressions that in optical cross-cut look like a radial striation. The hosts of the worm are chiefly rodents, less frequently dogs. Several cases of hepaticolosis in man have been described in India and the USA (North Carolina and New Orleans).

The parasite infests the liver, where the females deposit their ova in which infestive larvae develop without emerging from the host's body.

Man acquires the infection by ingesting food and drinking water contaminated with the ripe eggs of *Hepaticola* (*Capillaria*) *hepatica*. Animals become infested both in the above manner and by devouring infested animals, chiefly rodents. Contamination of the environment is due to carnivores (mammals, birds, and beetles) that devour rodents or their corpses. The *Hepaticola* ova pass through the digestive tract of these creatures without change and are voided with their feces (A. V. Pavlov, 1955).

The pathological anatomy and pathogenesis of this disease are known scantily. Abscesses, necrosis, and cirrhotic changes have been noted in the liver. Otto et al. (1954) described a fatal case of hepaticolosis that was accompanied by liver enlargement, ascites, fever, headache, abdominal pains, and an eosinophilic leukemoid reaction (30,000 eosinophils in 1 cu mm of blood). A piece of the liver was taken for examination at laparotomy; it was found to contain numerous *Hepaticola* eggs.

Hepaticolosis is very difficult to diagnose as the eggs of the parasite are very rarely passed in the stool. In doubtful cases biopsy specimens obtained by liver puncture have to be examined.

Prognosis may be very grave. Spontaneous destruction and absorption of the worms are possible, as their life-span is not long. Thus, they only live for 18 to 28 days in white mice (A. V. Pavlov, 1955). However, the eggs of these worms are preserved in the liver of the host to the end of the latter's life.

Treatment for *Hepaticola* (*Capillaria*) *hepatica* infection has still to be worked out. Chloroquine therapy has proved unsuccessful.



## TRICHOSTRONGYLIASIS (TRICHOSTRONGYLIDOSES)

---

Definition: a group of diseases caused by nematode worms of the family *Trichostrongylidae* (Leiper, 1912). These are helminths with a thin thread-like body; the mouth is unarmed, its direction anterior; the mouth capsule is either absent or rudimentary, and only in a few species is it comparatively well-developed; no cutting organs are present. The males possess a copulatory bursa with well-developed lateral lobes; the dorsal lobe is either undifferentiated or very poorly developed. The eggs are elongated and covered with a thin transparent shell; one end is rounded, the other tapers. Freshly-deposited eggs contain 16 to 30 blastomeres (morula stage). The eggs are 0.07-0.092 by 0.035-0.049 mm.

The trichostrongylids are parasites of the digestive system of vertebrates. The following species of this family have been discovered in man: 1) *Trichostrongylus axei* (Cobbold, 1879; Railliet a. Henry, 1909); 2) *T. colubriformis* (Giles, 1892); 3) *T. probolurus* (Railliet, 1896); 4) *T. orientalis* (Jimbo, 1914); 5) *T. skrjabini* (Kalantarian, 1928); 6) *T. vitrinus* (Looss, 1905); 7) *Haemonchus contortus* (Rudolphi, 1803); 8) *Mecistocirrus digitatus* (Linstow, 1906); 9) *Ostertagia ostertagi* (Stiles, 1892); 10) *O. circumcincta* (Stadelman, 1894).

The trichostrongylids infest the digestive tract of many herbivorous animals, chiefly horned stock (cattle, goats, sheep). Trichostrongyliasis caused by representatives of the genus *Trichostrongylus* have a high incidence in man, too. *Haemonchus* infection in man has been registered only several times in Brazil and Australia, *Mecistocirrus* was discovered in an inhabitant of Siang Yang. The chief source of trichostrongylidoses are herbivorous animals, man is less important. The eggs of the parasites are passed from the host in the feces. In the outer environment larvae develop and are hatched from the eggs; the larvae grow and develop and after some time become infestive. Infestation occurs through swallowing the larvae with contaminated water and food.

Little is known of the pathology and clinical features of these worm diseases. Gastrointestinal disorders have been noted, also secondary, occasionally severe, anemia and symptoms of functional disorders of the nervous system.

Diagnosis depends on the demonstration of the trichostrongylid ova in the stool.

Dehelminthisation is effected by means of tetrachloroethylene, chenopodium oil, or thymol, prescribed in the same manner as for ancylostomidoses.

Trichostrongyliasis is brought under control principally by the conduction of mass treatment of infested animals, sanitary disposal of infestive matter, and periodic alternation of grazing grounds.

## STRONGYLOIDOSIS

---

The causative agents of this morbid condition are nematode worms of the family *Strongylidae* (Baird, 1893). The condition is also known as esophagostomiasis.

The principal features of the worms of this family are the presence of a chitinous mouth capsule which carries no ventral cutting elements, but is usually surrounded by a corona of setae. The site of infestation is the alimentary tract or, in exceptional cases, the hepatic tissues. The following representatives of this family have been registered in man: 1) *Oesophagostomum brumpti* (Railliet a. Henry, 1905); 2) *O. stephanostomum* var. *thomasi* (Railliet a. Henry, 1909); 3) *Ternidens deminutus* (Railliet a. Henry, 1905).

The infection is acquired by ingesting the infestive larvae that develop in the outer environment from the ova voided with the feces of infested primates and humans; penetration of the larvae is also possible through the skin.

Having worked their way into the digestive tract of the host the oesophagostomum larvae burrow into the intestinal walls where peculiar nodules soon form around them. Six to eight days later the larvae emerge into the intestinal lumen, where they become attached to the mucosa, and there attain maturity. Infestation with these worms leads to the development of a dysenteric syndrome. *O. brumpti* was first discovered during a post-mortem examination of an African Negro. The parasites were located in cysts in the cecum and colon; these cysts were the size of a walnut and they contained a hemorrhagic substance; the immature females were 8.5-10.5 mm long.

*O. stephanostomum* was discovered by Thomas in 1910, in Brazil, in a deceased patient whose death had been preceded by symptoms of dysentery and peritonitis. It was subsequently found in inhabitants of French Guiana and Northern Rhodesia.

*Ternidens deminutus* is found in Africa among the population of Mozambique and Southern Rhodesia; the males of this worm are up to 9.5 mm long, the females up to 16 mm.

Diagnosis depends on the demonstration in the stool of ova resembling *Ancylostomatidae* eggs, and also of the parasites themselves following dehelminthisation by means of tetrachloroethylene.

Treatment is conducted with tetrachloroethylene, as for ancylostomiasis.

Prophylaxis is attained by proper personal hygiene and prevention of soil pollution by human feces.

# SYNGAMOSIS

---

Syngamosis is a morbid condition in man caused by infestation with nematode worms *Syngamus laryngeus* (Railliet, 1899). The worms are bright red, their terminal mouth capsules are well-developed. The walls of these capsules are supported by 6 long and 2 short chitinous crests that form 8 protruding teeth. The males and females are in permanent copulation. The male is 3 to 5 mm and the females 7 to 20 mm long. The eliptoid ova have a thin shell, their dimensions are 0.078-0.085 by 0.042-0.047 mm. The life-history of this helminth is not known.

*S. laryngeus* is a species which is usually a parasite of cattle, sheep, goats, horses, and in rare instances of man. Several cases in man have been reported from Brazil, the Antilles and Martinique.

Infestation with these worms is the cause of tracheobronchitis occasionally accompanied by hemoptysis and asthmatic suffocation.

Diagnosis rests on the demonstration of the eggs of the parasite in the sputum. Occasionally the worms, too, may be coughed up with the sputum. No study has been made of the treatment of this helminthiasis.

No prophylactic measures are known.

## GONGYLONEMIASIS

---

Gongylonemiasis (or gongylonematosis) is a condition due to infestation with *Gongylonema*, a genus of filarial nematodes, particularly *Gongylonema pulchrum* (Molin, 1857). The male of this species is 14 to 19.5 mm in length and 0.17-0.195 mm in breadth, the female 27-40 mm by 0.35 mm. The thick-shelled ova are transparent, their dimensions are 0.052-0.056 by 0.032 mm. The worms parasitise under the mucous membrane of the mouth and esophagus.

The biological properties of the *Gongylonema* are little known. The intermediate hosts of these helminths are dung-beetles and cockroaches.

A summary compiled by Feng, Tung and Su (1935) carries descriptions of 18 incidences of gongylonemiasis in man in the U.S.S.R., China, the U.S.A., Italy and other countries.

The location of the helminths under the oral mucosa causes hyperemia, at times the formation of papules, difficulty in moving the tongue. Feng et al. established (by esophagoscopy) hypertrophy, plication and bleeding of the esophageal mucosa, the presence in it of erosions and of a deep defect occupying an area of 1 sq cm. *Gongylonema* eggs were demonstrated in a biopsy specimen of mucosa. N. G. Kamalov (1953) reports that a patient of his complained of headache, irritability, and vomiting; all of these symptoms disappeared after the removal of a gongylonema from beneath the mucous membrane of his lower lip.

Gongylonemiasis of the lips and oral mucosa is diagnosed by the recovery of mobile, zigzaggy worms.

The parasites are removed surgically.

Treatment is conducted by ditrazin or hetrazan.

# GNATHOSTOMIASIS

---

Synonyms: larva migrans, creeping eruption.

The morbid condition defined as gnathostomiasis (or gnathostomosis) is caused by infection with nematode worms of the genus *Gnathostoma* (Owen, 1836); *G. spinigerum* (Owen, 1836), *G. hispidum* (Fedchenko, 1833).

*Gnathostoma spinigerum*. The male of this species is 11 to 25 mm in length, the female 15 to 54 mm. The definite hosts of the parasite are felines (both domestic and wild) and dogs, in whom the adult worms lie coiled in connective tissue tumours in the walls of the stomach. The first intermediaries are crustaceans, the second—certain species of fish: *Ophiocephalus argus*, *Ophiocephalus tadianus*, etc. Man occasionally acquires the infection by consuming raw fish.

A number of cases of gnathostomiasis have been reported from Japan, India, China, Thailand, and the islands of Indonesia.

In man the parasites are located in subcutaneous nodules, or wander freely in the skin, subcutaneous tissue, and submucosa, causing leukocyte infiltration—prevalently eosinophil—of the tissues.

The most frequent clinical characteristic of the disease is intermittent edema, less frequently linear dermatitis (hence “larva migrans” or “creeping eruption”). Expulsion of the parasite with the sputum has been reported.

The only prophylactic measure is to abstain from eating raw fish.

Treatment consists of the surgical removal of the worms.

*G. hispidum* has a peculiar triple colouring: its head-end is pinkish-red, the tail-end is greyish-brown with yellowish filarial marks. The male is 12 to 25 mm long, the female 25 to 45 mm.

The worm has been discovered in man in China and in Japan; it causes linear dermatitis (creeping eruption or larva migrans).

Prophylaxis is unknown.

Treatment is surgical.

## ABREVIATOSIS

---

Abreviatosis is a morbid condition caused by infection with the round-worm *Abreviata caucasica* (Linstow, 1902; Schultz, 1927), belonging to the family *Strongylidae*. It is also known under the synonyms of *Physaloptera caucasica* (Linstow, 1902) and *Ph. mordens* (Leiper, 1907).

The cuticula of this parasite is striated with transverse lines. The mouth is guarded by two lateral lips, each armed with several rows of teeth and two papillae.

The male measures 1.4-5 cm by 0.8-1 mm; its tapering tail curves ventrally and carries two unequal spicules and two lateral alae. The ventral surface of the tail is studded with cuticular scales in the form of wide, pointed plates. The female (2.4 to 10 cm by 1.4 to 2.8 mm) possesses four uteri. The smooth, thick-shelled elliptoid ova are 0.057-0.062 by 0.042-0.045 mm. *A. caucasica* lives in the esophagus, stomach and small intestine of certain primates and sometimes of man.

Abreviatosis has been registered in man in the Caucasus, Uganda, the South-African Republic, Nyasaland, and Central Africa. The life cycle of the *Abreviata* and, consequently, its epidemiology, have not been studied. It has been presumed that the intermediate hosts to *A. caucasica* are insects or other arthropods. The clinical symptoms are indeterminate. V. P. Podyapolskaya has reported that she observed a syndrome of gastric ulcer and deglutitory difficulties in a patient.

Diagnosis depends on the demonstration of the eggs of the worm in the stool. Chenopodium oil and heptylresorcinol are tentative dehelminthic agents.



## THELAZIASIS

---

Thelaziasis (or thelaziosis) is a morbid condition caused by *Thelazia*, a genus of threadlike nematodes. The principal species is *Thelazia callipaeda* (Railliet a. Henry, 1910), of the family *Thelaziidae* (Scryabin, 1915). The cylindric body of this worm tapers at both ends; its cuticula is transversely striated. The male measures 10.3-14.2 mm in length and 0.3-0.44 mm in breadth. Its thin tapering tail curves sharply and the two spicules it carries are very unequal. The right spicule is trough-like and measures up to 0.16 mm in length; the left spicule is an undulating flagellum reaching 1.87 mm in length. The adult female (12.24 to 18.3 mm by 0.4 to 0.45 mm) is packed with a great mass of ova and larvae in various stages of development. The young larvae lie spirally coiled in a thin sheath. As the larvae develop they move to the opening in the vulva, freeing themselves of their enclosing membranes. The eggs are 0.046-0.062 by 0.034-0.046 mm. The larvae measure 0.35 to 0.49 mm in length. *Th. callipaeda* has been discovered in man several times in China; the worm was found in the conjunctival sac, being the cause of conjunctivitis accompanied by severe pain in the eye. Recommended treatment is the injection of 2 per cent cocaine into the conjunctival sac.

No prophylaxis has as yet been worked out for thelaziasis, as the life cycle of its pathogen is indeterminate. It is possible that insects are the intermediate hosts to the parasites.

Another worm belonging to the *Thelaziidae* family that has been found several times in the human eye is *Th. californiensis*.

## DIOCTOPHYMOSIS

---

The causative agent of this worm disease is a nematode worm *Diectophyma renale* (Goeze, 1782). This is a bright-red parasite, the male of which measures 140 to 400 mm by 4 to 7 mm, the female 200 to 1000 mm by 5 to 12 mm. The entire surface of the thick brown shell of the ova is pitted; half of the circumference of each indentation is framed by an elevated ridge. The dimensions of the ova are 0.064-0.083 by 0.04-0.047 mm.

The infection is acquired through fish. The worm has been found in man in the U.S.S.R., Rumania, Egypt.

*Diectophyma renale* is a kidney worm localising in the pelvis of the kidney, the ureters and bladder; it may cause cystitis, pyelitis, and atrophy of the kidneys resulting in uremia.

Treatment is surgical.

# RICKETTSIOSES (RICKETTSIAL DISEASES)

---

Rickettsial diseases of man are a group of acute febrile diseases usually manifested by cutaneous eruptions and lesion of the small vessels. The diseases are caused by various species of *Rickettsii*. The pathogenic rickettsiae are minute, pleomorphic, gram-negative, mostly obligate intracellular parasites that live and multiply in arthropod tissues. Their characteristics as a group place them between bacteria and viruses. We shall here dwell only on the rickettsial diseases that are exclusively or prevalently restricted to the tropics and subtropics.

## ENDEMIC OR MURINE TYPHUS (RICKETTSIOSIS ENDEMICA MURINA)

Synonyms: Mexican typhus, tabardillo, urban typhus, shop t., flea t., rat t.

Endemic or murine (rat) typhus is an acute febrile disease, usually of a mild nature, characterised by a macular rash and a positive reaction to the Weil-Felix test with the *Proteus* antigen OX<sub>19</sub>.

### Historical data

The first clinico-epidemiological description was made by Hone in Australia in 1922-23, and subsequently by Maxcy in America in 1926. The etiological agent was discovered by Mooser in 1928. In the U.S.S.R. strains of *Rickettsii* of the Mooser type recovered from rats and human patients were first isolated by Y. G. Babalova in 1939 on the Black Sea coast. The clinical aspect and epidemiology of the disease were studied by Y. S. Gabrichidze, T. G. Shaparidze, A. Y. Alimov, A. A. Ivanov, P. F. Zdrovsky and his staff, and by other authors.

## **Etiology**

The disease is caused by *Rickettsia mooseri* (Monteiro, 1931), the characteristic feature of which is highly intensive multiplication in the protoplasm of the mesothelial cells of rodents and the presence of a specific toxic substance associated with the living microorganisms; the morphological form of the latter is either that of cocci or bacilli.

## **Epidemiology**

The source of infection are rats, mice, and their ectoparasites. Man acquires the infection either via the alimentary route with food contaminated with the urine of infested animals, or through fleas. The fleas ingest the *Rickettsii* when feeding on mice or rats; the microorganisms multiply in the flea intestine and are passed in the excreta. The infested fleas do not transmit the disease to man by biting him; transmission occurs through a specific "fecal virus" they excrete that contaminates the skin and upon drying up and dispersing settles on the mucous membranes of the mouth, nose and eyes.

Penetration of the *Rickettsii* through the skin is possible only through cutaneous lesions.

It is likewise possible that the infection may be transmitted to man from rodents via the bites of the murine tick *Bdelonyssus bacoti*.

## **Geographical distribution**

Endemic typhus is observed on the coasts of the Baltic, North, Mediterranean, Black and Caspian seas, in West and South Africa, in the southern states of the U.S.A., in South America, India, on the shores of the Persian Gulf, the Indo-China Peninsula, in China, Korea, on the Philippines, in West and North Australia. The principal foci are seaport cities of warm lands.

## **Clinical aspects**

The incubation period is 5 to 15 days. Onset is mostly acute, with headache, lumbar and joint aches, fever and chills. A prodromal period of several days is occasionally observed; during this period patients complain of general indisposition, weakness, headache. The fever may start with a rapid or gradual rise in temperature. Usually the pyrexial peak (38-40°) is reached at the end of the first week of the disease. The fever and chills are either remittent or continuous. The duration of the feverish period is, as a rule, 11 to 15 days, but in some cases it may be as short as 4-5 days, while in others it is protracted to 25 days (Fig. 105).

The next symptom of the disease is a rash, observed in 75 per cent of patients. The rash is localised on the chest, abdomen, extremities (including the palms and soles), often appearing on the fourth to seventh day of the disease. At first the rash is roseolous or macular, the diameters of

the separate spots measuring 2 to 5 mm; later it turns maculopapular or papular, in rare instances petechial. The rash persists for 4 to 10 days, sometimes longer.

No severe disorders of the nervous system are usually observed. However, occasional findings are meningeal symptoms, disturbance of coordination of the motor functions, general prostration, soporose conditions. Alimentary symptoms are a coated tongue and constipation. The liver does not become enlarged, nor is the spleen palpated. Respiratory

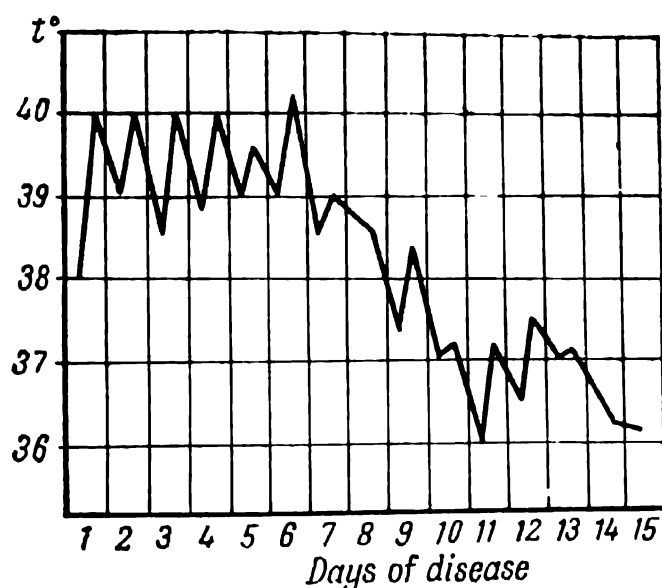


Fig. 105. Temperature curve in a case of murine typhus (P. F. Zdrodovsky a. Y. M. Golinevich, 1956).

system findings are bronchitis, occasionally bronchopneumonia. Cardiovascular symptoms: bradycardia, a slight fall in arterial pressure. The blood shows first leukopenia, then leukocytosis. Lymphocytosis and monocytopenia are observed through out the disease.

Complications are rare. However, American authors point to the possibility of furunculosis, otitis, parotitis, azotemia, skin necrosis, gangrene on the extremities.

### Diagnosis

The clinical features of endemic typhus are close to those of mild forms of epidemic typhus and therefore differential diagnosis between these diseases is quite difficult. S. M. Kulagin and S. A. Imamilov (1949) emphasise that a remittent fever, a roseolous-papular rash (frequently on the face, palms, and soles), leukopenia with lymphocytosis are symptoms more characteristic of endemic typhus than of epidemic typhus. As the Weil-Felix reaction with the *Proteus* antigen OX<sub>19</sub> is positive for both forms, endemic and epidemic typhus may be distinguished from each other only by means of differential serodiagnosis: simultaneous agglutination or complement-fixation tests with antigens obtained from *Rickettsia prowazeki* and *R. mooseri* (P. F. Zdrodovsky and Y. M. Golinevich, 1956). In endemic typhus the reaction with the *R. mooseri* antigen is positive at a higher titre than with the *R. prowazeki* antigen.

## **Prognosis**

In European sites the prognosis for endemic typhus is favourable; in South America, however, the course of the disease is more severe, and the mortality rate among persons over fifty is 2-3 per cent.

## **Pathology**

The pathology of endemic typhus is little known, as fatal cases are rare. Snyder (1955) states that the histopathologic pattern is probably similar to the one observed in epidemic typhus. The most characteristic features of the latter are vasculitis and thrombosis of the capillaries, small arteries and veins, and the formation of "typhus nodules" (vascular granulomas of Popov). It may, however, be presumed that in endemic typhus the above changes are much less pronounced.

## **Treatment**

Good effects are obtained with biomycin (aureomycin). The drug is given by mouth, 0.45 g every six hours; treatment is discontinued 24 hours after the temperature has returned to its normal level.

## **Prophylaxis**

Prophylaxis resolves into extermination of rats and mice, rat-proofing, control of fleas by the use of DDT, protection of food against contamination with rodent urine. In seaports there are special wharves for preventing passage of rats from ships to shore.

## **ROCKY MOUNTAIN SPOTTED FEVER (IXODO-RICKETTSIOSIS AMERICANA)**

Synonyms: mountain fever, typhomalarial fever (Russ.); tick typhus, exanthematic typhus of Sao Paulo, Tobia fever, Choix fever, pinta fever, black fever, blue disease (Engl.).

Rocky mountain spotted fever is an acute febrile disease with a characteristic rash and no primary lesion. The forms of this disease vary in severity in different sites and even in one and the same site in different years.

## **Historical data**

The disease was first singled out as a nosologic entity by Maxcy in 1899 in the U.S.A. and subsequently subjected to a circumstantial laboratory study by Ricketts and King (1906-09). The pathogen was discovered in 1906 by Ricketts and described in detail by Wohlbach in 1919. Ricketts also discovered the vectors of the infection—various species of ticks.

## Etiology

The etiological agent is *Dermacentroxenus rickettsi* (Wohlbach, 1919).

The microbe is localised intracellularly, penetrating not only into the protoplasm of cells, but into their nuclei as well. In man it is mostly concentrated in the endothelium and the muscular cells of the blood vessels. This organism is highly polymorphous, appearing in homogenous bacilliform clumps as fine rods with chromatin inclusions, in lanceolate forms and as infinitesimal formations.

## Epidemiology

The vectors of the infection are *Ixodidae* and *Argasidae* ticks (Fig. 106) in which the rickettsiae are preserved for years and are passed transovarially to progeny. The existence in natural conditions of spontaneously infested ticks, which do not feed on man, has been proved. Wild animals may

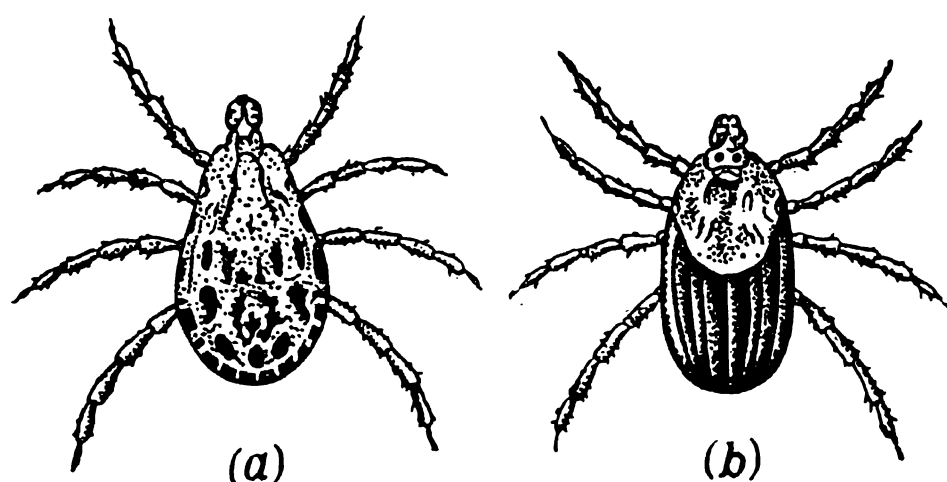


Fig. 106. One of the vectors of Rocky Mountain spotted fever, the tick *Dermacentor andersoni* (Brumpt, 1949)

a — male; b — female

also serve as transient reservoirs of the infection (small rodents, guinea pigs, rabbits, dogs, and possibly also large mammals), contracting the virus through tick-bites. Consequently, Rocky Mountain spotted fever is an endemic disease with natural foci.

The infection is transmitted to man through the bites of ticks, mostly in pasture grounds (therefore the disease prevalently affects farmers and agricultural labourers).

## Geographical distribution

Rocky Mountain spotted fever occurs throughout the USA, Canada, Mexico, Brazil, Colombia.

## Clinical aspects

The incubation period is from 2 to 14 days. The onset of the disease may be preceded by premonitory symptoms: malaise, headache, loss of appetite, light chills. In other cases a severe headache appears suddenly,

accompanied by pains in the muscles and joints, vomiting, nosebleed; the temperature goes up rapidly. The total duration of the feverish period is usually 2-3 weeks, sometimes less, sometimes more. The temperature may go up to 40-41° in the evenings, and be 0.5-1.5° less in the mornings. The fever resolves by lysis, either accelerated (in 3-4 days) or slow (7-8 days) (Fig. 107).

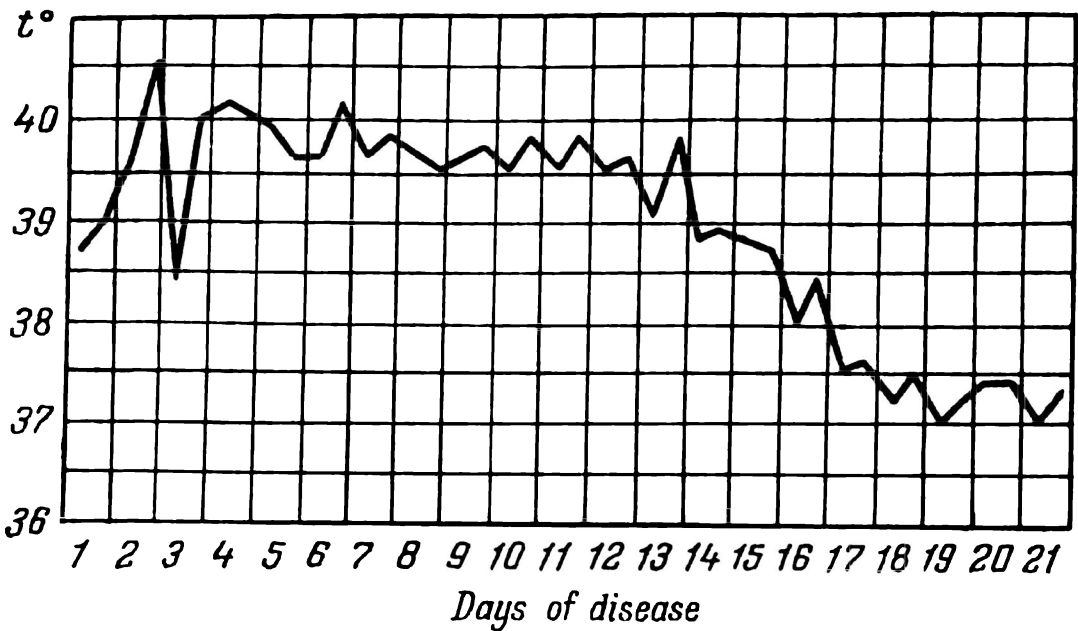


Fig. 107. Temperature curve in case of Rocky Mountain spotted fever.  
Infection contracted in laboratory (Brumpt, 1949)

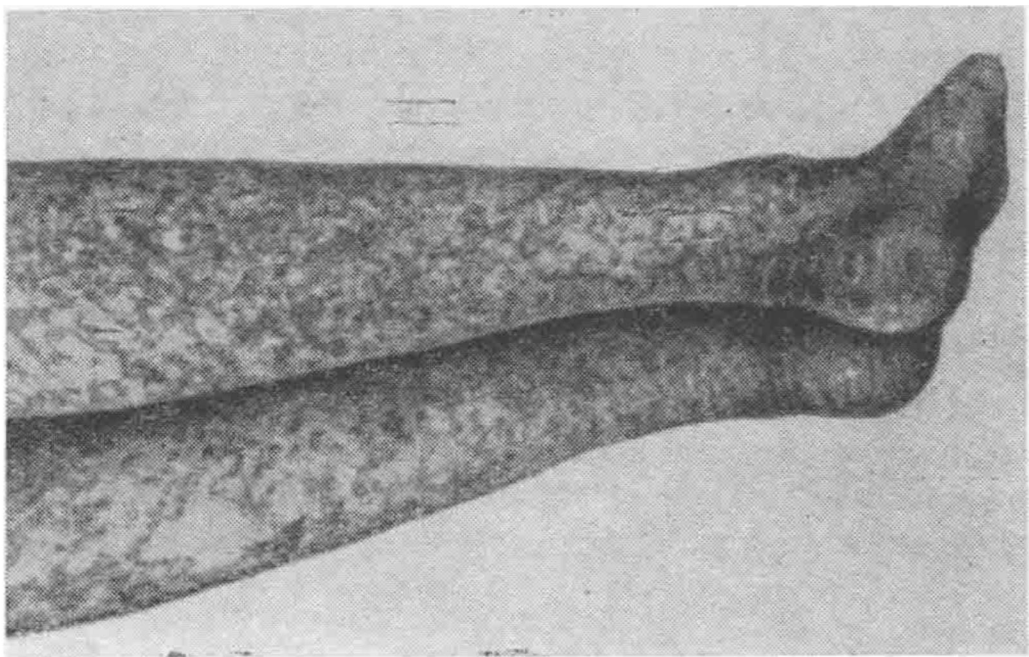


Fig. 108. Hemorrhagic rash in case of Rocky Mountain spotted fever (Spencer a. Parker, 1930)

On the second to fourth day of the disease a rash resembling early measles appears; it is soon replaced by the typical maculopapular eruptions. The latter appear on the elbows and wrists and rapidly spread to the upper and lower extremities, including the palms and soles, to the chest, and occasionally to the face and scalp. Gradually the rash turns petechial, in severe cases the eruptions merge (Fig. 108). Occasionally necrotic areas



appear on the genitalia and the soft palate. Central nervous system symptoms are insomnia, headache, in severe cases delirium, mental disorders, convulsions, increased tendon reflexes, pathologic reflexes, sometimes even coma. Paralysis of the cranial nerves, paraplegia and hemiplegia have been described.

The spleen is enlarged and firm. Jaundice and enlargement of the liver are frequent. Cardiovascular symptoms: bradycardia, in severe cases, on the contrary, tachycardia.

Frequent complications are pneumonia, phlebitis, iritis, hemorrhages, severe lesions of the nervous system.

Recovery is slow even in mild forms of the disease; in severe cases complete recovery may take many months.

### **Diagnosis**

Rocky Mountain spotted fever is not easy to diagnose, for its clinical features have much in common with endemic and epidemic typhus. The laboratory methods of diagnosis are the complement-fixation test with an antigen from the rickettsial pathogens of the disease, infection of animals with the patient's blood, and neutralisation of the virus with serum obtained from the blood of the patient.

### **Prognosis**

Prognosis for marked and severe forms of Rocky Mountain spotted fever is very grave. There are sites of the disease in which termination is fatal in 80 per cent of cases, while in other sites it is 5-10 per cent. And what is more, it has been noticed that sometimes the mortality rate becomes high even in the areas where it was previously relatively low.

### **Pathology**

The most characteristic macroscopic changes are hemorrhages into the tissues of the scrotum, testes and their appendages; necrosis is not uncommon. Microscopic findings are thrombosis of the small peripheral vessels, degenerative changes in their endothelium and in the smooth muscles owing to the intracellular penetration of the rickettsial organisms; infiltrates appear on the vessels in the form of nodules and sleeves consisting of lymphocytes and plasmacytes.

### **Treatment**

Specific therapy for Rocky Mountain spotted fever is applied with antibiotics—chloromycetin, aureomycin (biomycin), terramycin. Cox (1955) recommends peroral administration of one of the above antibiotics in daily doses of 2-3 g; the daily dose is divided into 6-12 equal portions taken every 2-4 hours. Treatment is discontinued 24-48 hours after the temperature falls. The fever is usually curtailed in 48 to 72 hours. Should a relapse occur antibiotic treatment is repeated.

## Prophylaxis

Prophylactic measures include special clothing as protection against tick-bites, and application of insectifuges (dimethyl phthalate and dibutyl phthalate). Upon returning from tick-ridden areas the body and clothing must be thoroughly examined and the ticks removed with forceps or paper and burnt; after handling ticks the hands should be carefully washed. A special vaccination is also employed for prophylaxis. However, the best safeguard against Rocky Mountain spotted fever is proper soil cultivation throughout the territory.

### BOUTONNEUSE (MARSEILLES) FEVER (IXODO-RICKETTSIOSIS MARSELIENSIS)

Synonyms: exanthematous fever, infective epidemic exanthema, eruptive fever.

Boutonneuse fever is a benign acute febrile disease characterised by a specific maculopapular eruption and a characteristic primary lesion, or *tâche noire*, on the skin at the site of the infecting tick-bite.

### Historical data

The first clinical description of boutonneuse fever as an independent disease was made by Conor and Bruch in 1910 in Tunisia. It was rediscovered in 1925 by Olmer in Marseilles. Durand and Conseil (Tunis, 1930) established that *Rhipicephalus sanguineus* (the canine tick) was the vector of the disease. The etiological agent was discovered by Caminopetros in 1932 and described that same year by Brumpt. In the U.S.S.R. Marseilles fever was first discovered by M. F. Andreyev and studied by A. Y. Alymov in the years 1936-39.

### Etiology

The disease is caused by the rickettsial organism *Dermacentroxenus conori* (Brumpt, 1932) (synonyms: *Rickettsia conori*, *Coxiella conori*). This organism is capable of multiplying in cellular nuclei. It is demonstrable in the blood of patients, in the primary lesion at the site of the tick-bite, and in the eruptions on the skin.

### Epidemiology

The disease is transmitted by the canine tick *Rhipicephalus sanguineus* (Fig. 109).

This tick is both the vector and natural reservoir of the infection, which it passes on to its progeny transovarially. No authentic hosts of the virus of Marseilles fever have been found to date among mammals. Even dogs, the animals on which the ticks feed, have proved very resistant to the in-

fection; it was only producible in young pups, and asymptomatic even then.

Man acquires the infection through the bite of an infested canine tick; very rarely the virus is transmitted from the tick to the conjunctiva.

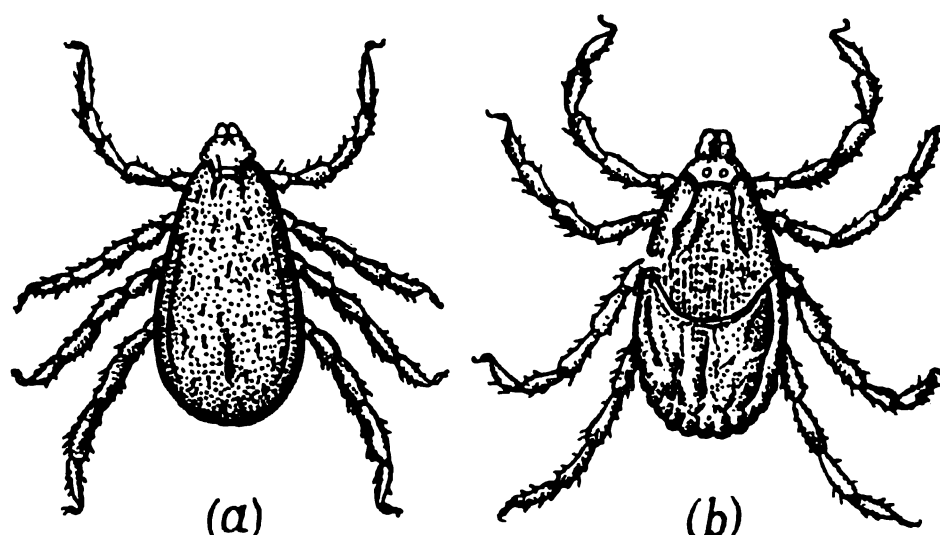


Fig. 109. The canine tick *Rhipicephalus sanguineus*, vector of  
Marseilles fever

*a*—male (B. I. Pomerantzev); *b*—female (M. F. Pospelova-Strom)

The foci of the disease are associated with the area of distribution of canine ticks. Boutonneuse fever never appears as an epidemic; it is restricted to sporadic cases, as the vectors rarely attack man, and the susceptibility of man to the infection is very low.

### Geographical distribution

Endemic sites of boutonneuse fever exist in the coastal regions of the basins of the Mediterranean, Black and Caspian seas, and also in India and tropical Africa.

### Clinical aspects

The incubation period lasts 5 to 7 days, rarely longer—up to 18 days. Onset of the disease is acute, with chills followed by an elevation of the temperature to 40 °C (Fig. 110), headache and pains in the muscles and joints. The duration of the feverish period is usually 10 to 14 days, sometimes longer (up to 22 days). Throughout the disease, from beginning to end, the so-called primary lesion (*tâche noire*) is often seen on various parts of the body in the area of the tick-bite; this lesion is a small ulcer, 2 to 5 mm in diameter, covered with a necrotic crust and surrounded by a dark-red zone (Fig. 111). Penetration of the conjunctiva by the rickettsii leads to conjunctivitis, edema of the entire conjunctiva, keratitis. A rose-oleous or macular eruption appears on the third or fourth day of the disease; the eruption swiftly spreads over the entire body, including the face, palms, and soles; soon it becomes maculopapular; occasionally second-

ary petechiae appear. In some patients the eruptions may be very scanty. Occasionally discrete small red spots appear on the palate.

Nervous system findings are tremor of the lips, tongue, hands, sometimes soporose states, rarely violent delirium, meningeal symptoms (M. F. Andreyev, 1941).

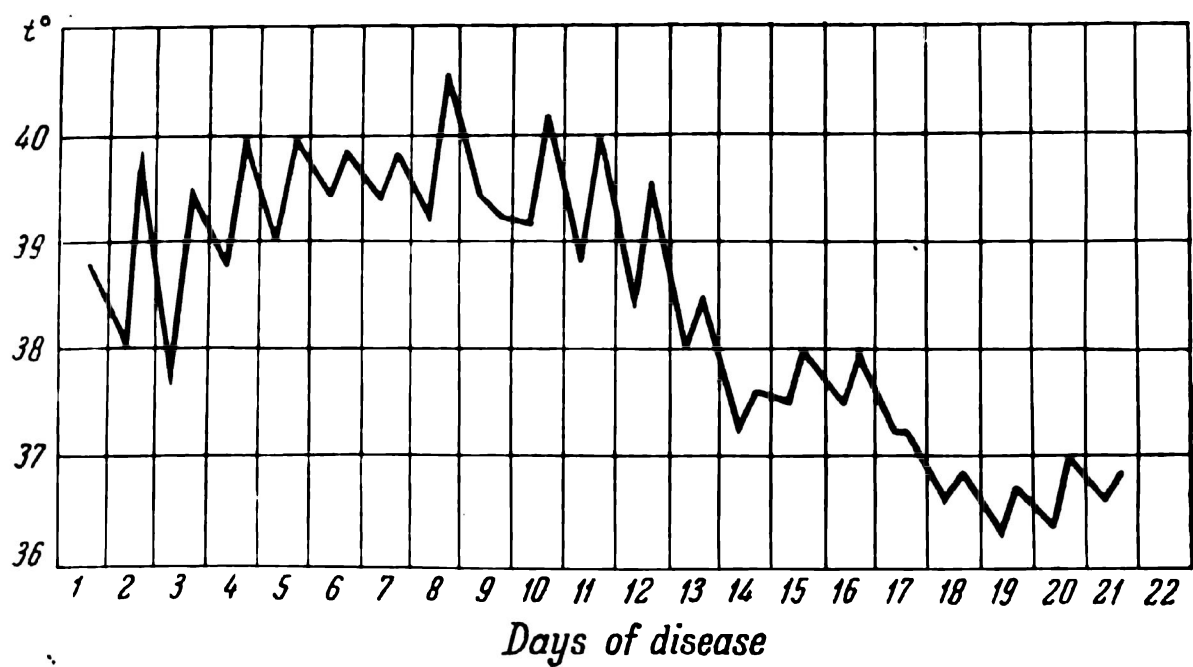


Fig. 110. Temperature curve in case of boutonniuse fever (P. F. Zdrodovsky a. Y. M. Golinevich)

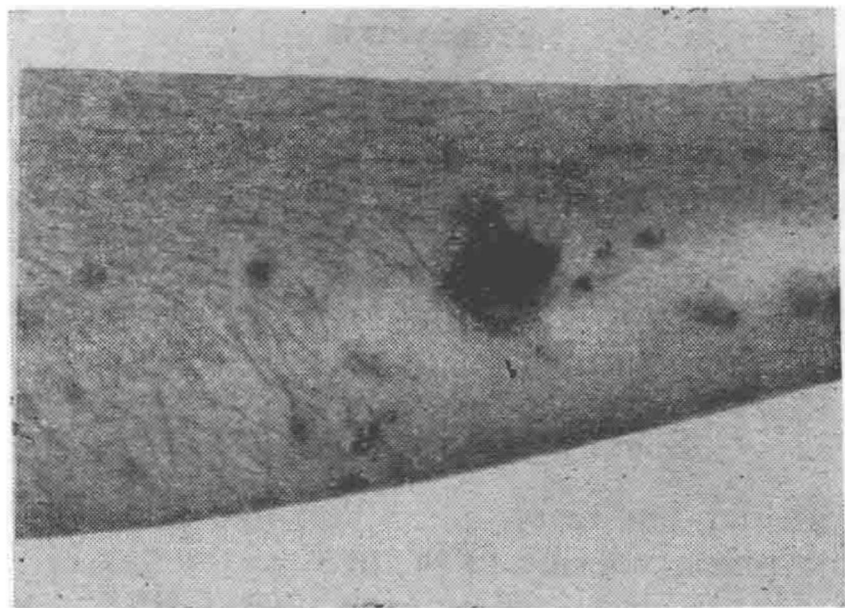


Fig. 111. Primary lesion in area of tick bite (A. S. Avetisova)

Findings in the digestive system: white-coated tongue, constipation, rarely – diarrhea. The spleen is sometimes enlarged.

**Diagnosis**

Boutonniuse fever is distinguished from epidemic and endemic typhus and Rocky Mountain spotted fever by the presence of a primary lesion (*tâche noire*) with regional lymphadenitis. The most reliable methods of

laboratory diagnosis are complement fixation with the undiluted antigen obtained from *D. conori* (P. F. Zdrodovsky and Y. M. Golinevich, 1956).

The Weil-Felix reaction is of no diagnostic value as it only becomes positive in the convalescent period.

### **Prognosis**

Boutonneuse fever usually follows a benign course. According to the data of Soviet authors lethal terminations are rare.

### **Pathology**

The histological examination of biopsy specimens of skin taken from eruptive sites has shown maculopapular eruptions to be associated with a swelling of the vascular endothelium and with perivascular infiltration of lymphocytes, monocytes, occasionally polymorphonuclear leukocytes.

### **Treatment**

Therapy is conducted with biomydin (aureomycin) and terramycin, as for Rocky Mountain spotted fever.

### **Prophylaxis**

Prophylaxis is effected by gaining control of canine ticks. This is done by rubbing dogs with 10 per cent DDT ointment. Stray dogs are exterminated. Ticks are destroyed in the yards of houses where there are dogs.

## **SOUTH AND EAST AFRICAN TICK-BITE FEVERS (IXODO-RICKETTSIOSES AFRICANAE)**

### **South African tick-bite fever**

South African tick-bite fever is a typhus-like disease with or without eruptions, with a primary lesion in the area of the tick-bite.

The disease was first described by McNaught in 1911, and in that same year independently by Sent-Anna.

Pinkerton (1942) isolated the causative agent of South African tick-bite fever under the name of *Dermacentroxenus rickettsi* var. *pijperi*; however he recommended this name provisionally, as there were no sufficiently clear distinctions between the pathogens of South African tick-bite fever and boutonneuse fever (cited from P. F. Zdrodovsky and Y. M. Golinevich, 1956).

The reservoir and vectors of the virus are *Amblyomma heabreum* and *Haemaphysalis leachi* ticks, and, most probably, also other species of ticks. The virus is transmitted to man through the bite of an infested tick.

The disease is widespread in the southern part of Africa.

The clinical aspect of South African tick-bite fever is very similar to that of boutonneuse fever, so that certain authors consider these diseases to be identical.

The incubation period lasts approximately one week.

A primary lesion is formed at the site of the infestive tick-bite—a painless red spot 2-5 cm in diameter, with a black necrotic area in its centre; the regional glands are enlarged and tender.

In cases of mild forms of the disease the fever lasts for only 3-4 days; it is accompanied by moderately painful headache and no eruptions. In severe forms the temperature rises to 39-40°C, acute headache and photophobia are observed, and, in some instances, also stiffness of the occipital muscles and delirium. The fever lasts, on the average, 10-12 days. On the fifth or sixth day of the disease a macular or papular rash usually appears on the entire body, including the palms and soles; occasionally only discrete papules are observed on the chest, abdomen and upper extremities.

No clinical distinction between South African tick-bite fever and boutonneuse fever is possible. Among the various laboratory tests best results are obtained with the rickettsial agglutination and complement-fixation reactions. The Weil-Felix test with *Proteus* antigens OX<sub>2</sub> and OX<sub>19</sub> is not clearly specific, and the reaction becomes positive only at a late stage of the disease.

Prognosis is favourable.

Prophylactic measures are the same as for Rocky Mountain spotted fever and boutonneuse fever.

Treatment: a specific effect is obtained with aureomycin.

### **East African tick-bite fever**

This is an acute febrile disease accompanied by skin eruptions, the formation of a primary lesion, and regional lymphadenitis. It was distinguished clinically by Gilks in 1914. The rickettsial nature of the causative agent was first proved by Tonking in 1932. In 1930, Roberts established the transmission of the infection through the canine tick *R. sanguineus*.

The pathogen is a rickettsial organism of the genus *Dermacentroxenus*. P. F. Zdrodovsky and his associates proved that the Kenya strain of this rickettsia is identical with the *D. conori* strain (the causative agent of boutonneuse fever) isolated on the Black Sea coast.

The disease is common in Tanganyika, Kenya, Uganda, Ethiopia, Somali.

The clinical features, prophylaxis and treatment are the same as for boutonneuse fever.

## NORTH QUEENSLAND TICK TYPHUS (IXODO-RICKETTSIOSIS AUSTRALIENSIS)

North Queensland tick typhus is a benign type of typhus first described clinically by Andrew, Bonnin and Williams in 1946, in Australia.

The causative agent is a rickettsia of the genus *Dermacentroxenus*. The epidemiology of the disease is little known. The infection is transmitted by ticks, but of what species is not clear. The disease is widespread in Australia.

A seven- to ten-day incubation period is followed by approximately one week of fever with malaise and headache terminating by lysis. A primary lesion with regional lymphadenitis and a rash are observed.

## TSUTSUGAMUSHI DISEASE (JAPANESE FEVER) (RICKETTSIOSIS TSUTSUGAMUSHI S. NIPPONICA)

Synonyms: scrub typhus, Japanese river fever, Queensland coastal fever, Malayan typhus, Sumatran mite typhus, kedane fever, mite typhus.

The tsutsugamushi disease is transmitted by bloodsucking mites. This acute febrile disease is characterised by a primary lesion or eschar, headache, a rash and a positive reaction to the Weil-Felix test with *Proteus* OX<sub>k</sub>.

### Historical data

The disease has been known since ancient times. It was described in China in the 3rd century before our era by Keh-Hung, and in Japan in 1810, by Hashimoto. In 1906-09 Kitasima and Miyima proved that the larval forms of a species of *Trombicula*—velvet mites—were the vectors of the disease. The rickettsial nature of the etiological agent was revealed by Nagayo and other authors in 1930-31.

### Etiology

The etiologic agent is *Rickettsia orientalis* (Nagayo, 1930). This micro-organism is capable of multiplying in the cellular plasm, but does not penetrate into the nuclei. When cultivated in egg media it forms a toxin. These rickettsii resemble minute diplococci or short bacilli.

### Epidemiology

The vectors and natural reservoirs of the infection are certain species of velvet mites *Trombiculae*: *Tr. akamushi*, *Tr. deliensis*, *Tr. schueffneri* (Fig. 112). The infection is transmitted from generation to generation of mites transovarially. Spontaneous infection in field-mice has been proved. Consequently, tsutsugamushi is an endemic disease with natural foci. The infection is transmitted to man through the bite of an acarus—the blood sucking larvae of *Trombicula* mites; this occurs in the scrub and jungles,

where the mites live in moist soil and detritus. In their search for blood the larvae crawl up plants and from them pass on to man and animals.

A high incidence of tsutsugamushi disease is possible among the population; this usually occurs in war-time, when many people come into close contact with plants in the scrub and jungles, the natural environment of the trombiculids.



Fig. 112. Larvae of the red-bodied tick *Trombicula akamushi* (Brumpt), vectors of tsutsugamushi disease

### Geographical distribution

Tsutsugamushi disease is widespread in Japan, South Korea, China, including the Island of Taiwan and the Pescadores, in Viet-Nam, Malaya, Burma, India, Ceylon, the Philippines, Borneo, Java, Sumatra, Sulawesi (Celebes), New Guinea, Australia (northern part of Queensland) (Fig. 113).

### Clinical aspects

The incubation period varies from 6 to 21 days, lasting 10 to 12 days on the average. The disease sets in abruptly with fever and chills, severe headache, and general enlargement of the lymph nodes; the fever may also be preceded by general indisposition, moderate headache, loss of appetite. The temperature peak (40-40.5°C) is usually attained by the 3rd or 4th day of the disease. The duration of the feverish period (terminating by lysis) is commonly 2-3 weeks (Fig. 114).

The primary lesion at the site of the insect-bite (on the hands, arms, in the axilla, on the trunk and other parts of the body) appears at the onset of the fever in the form of an erythematous infiltrate with a spongy vesicle that after several days turns into a superficial ulcer 0.3-2 cm in diameter (the eschar), frequently with a necrotic crust in the centre; the regional lymph nodes become enlarged. In some instances the primary lesion does not develop, or is imperceptible.

On the 4th to 6th day of the disease a macular rash appears on the trunk, occasionally also on the extremities; after some time this rash takes on a maculopapular aspect; sometimes hemorrhagic spots are observed on



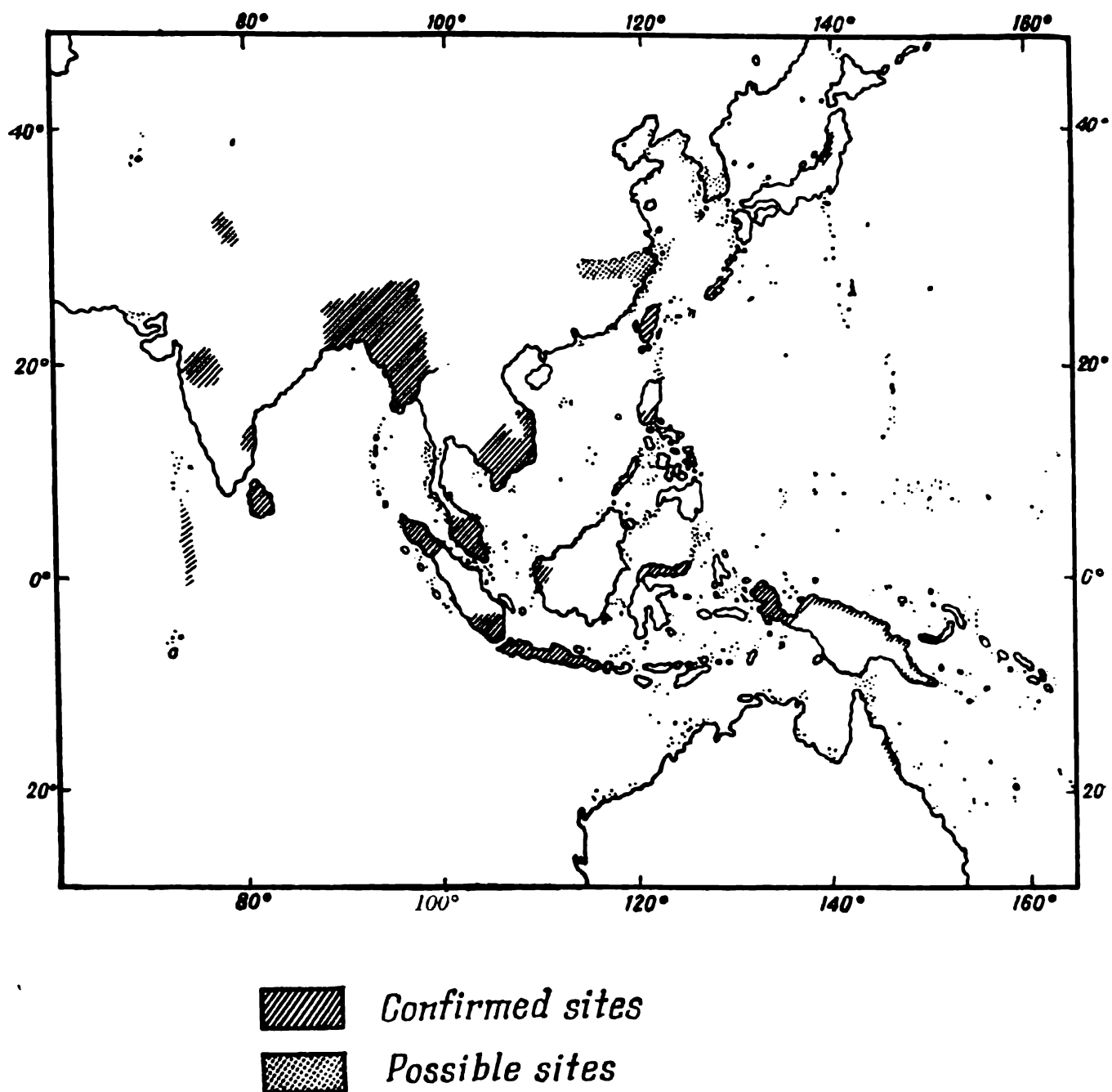


Fig. 113. Geographical distribution of tsutsugamushi disease (Black et al., 1945)

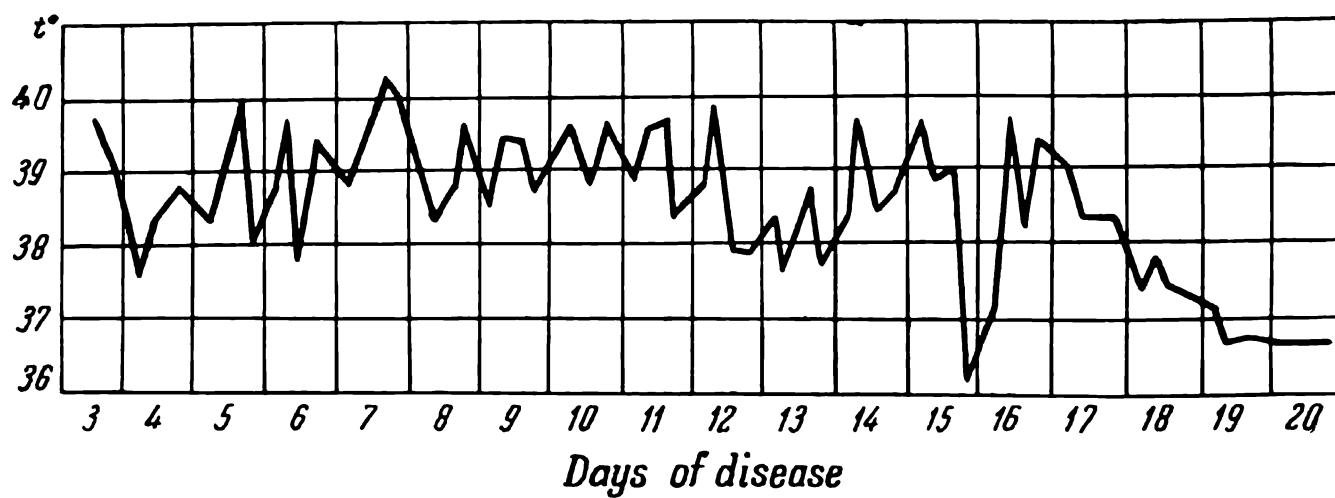


Fig. 114. Temperature curve in severe form of tsutsugamushi disease (Black et al.)

the skin. Frequent respiratory symptoms are bronchitis and atypical pneumonia. Cardiovascular symptoms: in severe cases acute tachycardia with extrasystole and hypotension, occasionally vascular collapse, vascular thrombosis and hemorrhages occur. Central nervous system symptoms: neuropsychic disturbances are not uncommon. In many cases the spleen is enlarged. Blood tests show no characteristic changes. The white blood count remains, as a rule, within a normal range, leukocytosis only appearing with a secondary infection. Anemia is rare. In some patients hypoproteinemia is observed, due chiefly to a decrease in the blood albumin level.

### **Diagnosis**

The diagnosis of tsutsugamushi disease is based on clinical features, epidemiological data, the Weil-Felix test, and the recovery of the agent from the patient. The Weil-Felix test is done with the *Proteus* antigen OX<sub>k</sub> that is positive in the second week of the disease. The pathogen is recovered by injecting mice intraperitoneally with 0.1-0.2 ml of the patient's blood. The majority of the mice so injected perish within two weeks of demonstrable generalised rickettsiosis. Laboratory tests are of no avail in early diagnosis of the disease, therefore they are important only in revealing the first cases.

### **Prognosis**

In severe forms prognosis was very grave prior to the introduction of antibiotics. In some endemic sites of tsutsugamushi (e. g., in Japan) lethal outcomes were registered in 30 per cent of cases on the average, and among patients aged 60 years and older even in 59 per cent. Death usually occurred at the end of the second week of the disease. The administration of antibiotics has almost entirely eradicated mortality.

### **Pathology**

Postmortem findings: plethoric viscera, interstitial pneumonia, frequently glomerulonephritis, acute focal or diffused interstitial myocarditis; CNS symptoms in the form of meningitis and encephalitis are not uncommon; symptoms include dispersed focal vasculitis and perivascularitis, most marked in the brain, kidneys, lungs and heart.

### **Treatment**

Specific agents for the treatment of tsutsugamushi disease are chloromycetin (levomycetin), aureomycin (biomycin) and terramycin.

Smadel (1955) recommends the administration of one of the above antibiotics perorally according to the following plan: first a shock dose of 3 g, then 0.5 g every six hours until the temperature falls to normal. Usually 5 g of the preparation within 24 hours suffice, but in severe cases treatment is continued for 2-3 days.

Under the effect of antibiotics the temperature returns to normal two days after institution of treatment. In relapses the antibiotics are prescribed again in total doses of 3-5 g per cycle of treatment. A relapse may be avoided by giving 3 g of one of the above-mentioned antibiotics in a single dose on the sixth day after completing the first cycle of treatment. Penicillin is ineffective, sulfa drugs are contraindicated.

### **Prophylaxis**

The disease is combated by clearing and tilling the areas inhabited by the *Trombicula* mites and by wearing clothing impregnated with a 5 per cent emulsion of dimethyl phthalate or dibutyl phthalate in a 2 per cent soap solution as protection against the mites.

Good results are obtained with chemoprophylaxis: healthy subjects are given antibiotics in 3-g doses over weekly intervals. Sometimes chemoprophylaxis is combined with the inoculation of vaccines containing living rickettsia.

### **Q FEVER OR PNEUMORICKETTSIOSIS (RICKETTSIOSIS Q SEU PNEUMORICKETTSIOSIS)**

Q fever is an acute febrile disease often accompanied by specific pneumonitis, no rash or only a sparse rash; in distinction from other rickettsioses the reaction to the Weil-Felix test is negative. The disease is also called "nine-mile fever" (U.S.A.).

### **Historical data**

Pneumorickettsiosis was identified as a separate disease by Derrick in 1935-37. The nature of the disease was not clear at that time, therefore he called it Q fever, taking the first letter of the word "query". In 1938, Derrick succeeded in isolating the virus from the blood of patients, while Burnet and Freeman proved that this virus was a rickettsial organism with filtrable forms. Derrick proposed calling the causative agent of Q fever *Rickettsia burneti* (synonym *Coxiella burneti*). Subsequently Derrick and other authors isolated these rickettsii from rats and other small Australian animals, and also from rat ticks, and a calf was experimentally infected (cited from P. F. Zdrodovsky and Y. M. Golinevich, 1956).

### **Etiology**

The etiologic agent of Q fever is *Rickettsia burneti* (Derrick, 1939). The forms most typical are coccoid, although bacillary and thread-like forms, as well as minute streptococcal forms, are also encountered. A characteristic feature of *Rickettsia burneti* is the formation of dense intracellular colonies (in the cytoplasm) and the existence of filtrable forms.

## **Epidemiology**

The basic source of infection are large and small horned stock, but it may also be transmitted by horses, mules, donkeys, and dogs. Moreover, spontaneous infection has been found in natural conditions in ticks and in certain wild mammals – opossums, gophers, gerbils, etc. Mammals shed the rickettsia with their milk and excreta, in the placenta and amniotic fluid. The ticks transmit the infection through their bites and pass the virus with their excreta.

Man acquires the infection by drinking the milk of infested animals and by consuming food or drinking water contaminated with their excreta. Infection may be contracted by contact with infested animals and the objects around them, as well as with farm produce (wool, etc.). The agent of Q fever is very stable, and is particularly resistant to desiccation. Consequently, the infection may also be transmitted aerogenously by inhaling rickettsiae-containing dust. The rickettsiae may be transferred over great distances from the site of the disease with straw, cotton-wool, wool and other farm goods. It is also not improbable that man is infected by the bites of ticks and by their excreta. Transmission of the disease from man to man is exceptionally rare.

The entrance points of the infection are the mucous membranes of the digestive tract, the respiratory system, the eyes, and also the skin (even if it is intact). Moreover, the Q fever pathogen is highly infectious and infestive, and this is one of the basic causes of its widespread incidence among animals, of heavy outbreaks among humans, and of a number of cases of laboratory infection.

## **Geographical distribution**

Epidemics of Q fever have been registered, besides Australia, in the U.S.A., Africa, and a number of European and Asiatic countries, including the U.S.S.R.

Indeed, it must be acknowledged that this disease is global.

## **Clinical aspects**

The incubation period lasts for 18 to 26 days. The onset of the disease is usually acute, and is accompanied by chills and a rapid rise in temperature, reaching 39-40°C within 2 to 4 days. As a rule the fever is of a remittent nature, much less frequently it is continuous (Fig. 115). Patients complain of severe headache, pain in the supraorbital region, muscles, joints, and occasionally also in the chest, and of coughing. Upon examination of the patient marked lassitude, flushed face and conjunctivitis are observed; the lymph nodes are frequently enlarged. The skin is usually clear; in rare cases solitary roseolous eruptions are discovered.

Frequent respiratory symptoms are bronchitis, pneumonia, and occasionally pleurisy. The incidence of pneumonia in Q fever ranges, according

to various authors, from 5 to 83 per cent of cases. The principal causes of such a divergence are the routes of infection characteristic of particular outbreaks and the different methods of medical examination. Pneumonia is most frequent in aerogenous infections. It is very difficult to diagnose rickettsial pneumonia by means of physical methods of examination; roentgenoscopy is the chief means of determining this condition. S. A. Reinberg and co-workers (1956) employed this method and revealed pathologic changes in the lungs of 10 out of 27 Q fever patients. These authors

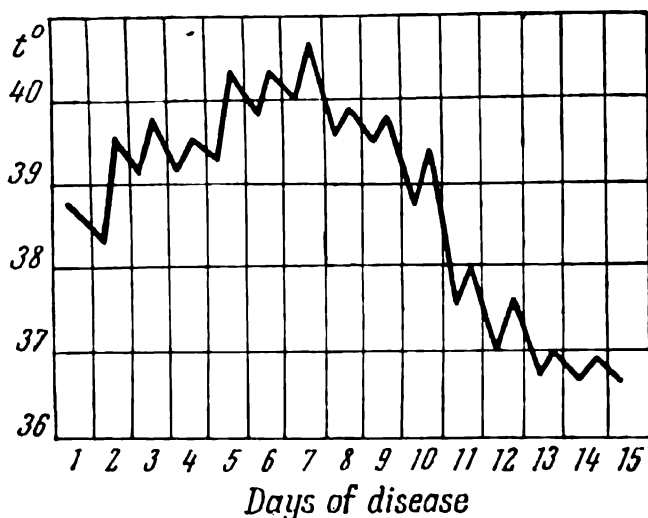


Fig. 115. Temperature curve in a case of Q fever (D. G. Teverovskaya)

hold that a characteristic feature of Q fever is the presence of a usually rounded, faintly outlined, light shadow of an exudative pneumonic type on the periphery of the pulmonary field; the shadow is not infrequently segmented. Usually the pneumonic shadow is a solitary one, but multiple bronchopneumonic sites have also been noted. The upper lobe of the lung is more frequently affected, the lower one less frequently so, the middle lobe still rarer. The pneumonia is often accompanied by an enlargement of the lymph nodes at the base of the lung. Pleurisy associated with Q fever is commonly of the fibrinous type. Occasionally a slight exudate is present. Cardiovascular findings are a certain dullness of the heart sounds, moderate bradycardia, a slight hypotension; digestive system findings are poor appetite, coated tongue, infrequently nausea and vomiting. According to the data of the authors the spleen is enlarged, though it remains soft, in 80 per cent of cases; it protrudes 1-2 cm from under the left subcostal rim. Enlargement of the liver is rare. Hepatitis with marked jaundice is occasionally observed. Blood counts show a slight leukopenia at the onset of the disease, while subsequently leukocytosis and neutropenia with a prevalence of younger forms are registered; monocytosis is not uncommon. The present authors have observed up to 4 per cent of plasmacytes. The ESR is frequently accelerated.

The duration of the febrile period of Q fever is from one day to 3-4, or even more, weeks, but it is 2 to 10 days on the average; the fever is resolved by lysis or crisis. In some cases a relapse of the disease occurs in 4 to 8 days after the normalisation of the temperature; during the relapse the feverish period lasts for 4-10 days (I. N. Shchetinina, 1955).

The pathological changes in the lungs persist for some time after the temperature has returned to normal. S. A. Reinberg and co-workers observed residual signs in the lungs for as long as 80 to 106 days by means of X-rays.

Meldolesi (cited from P. F. Zdrodovsky and Y. M. Golinevich, 1956) distinguishes the following clinical forms of Q fever: 1) influenza-like form; 2) septic form, frequently complicated by bronchopneumonia, exudative pericarditis, pleurisy, phlebitis, hepatitis, pancreatitis, orchitis; 3) acute bronchopneumonic form; 4) subacute pulmonary form; 5) neurological form accompanied by meningeal symptoms, radiculitis, neuritis, bulboencephalitic lesions; 6) pseudo-brucellosis form with undulating fever; 7) subfebrile form; 8) latent form.

### **Diagnosis**

In distinction from other rickettsial diseases Q fever is characterised by a negative Weil-Felix reaction, frequent development of pneumonia, absence of a primary lesion and, in the overwhelming majority of cases, absence of any rash.

Laboratory diagnosis is established by means of agglutination and complement fixation with an antigen from *Rickettsia burneti*; these tests are positive within 7 to 20 days after the onset of the disease. Of late the subcutaneous allergic test has also been introduced into diagnostic practice.

### **Prognosis**

Prognosis is favourable, mortality is very rare.

### **Pathology**

Lethal termination of Q fever is very uncommon, consequently the pathology of this disease in man has been studied very little. Only the presence of pneumonic sites in the lungs has been noted.

### **Treatment**

The infection responds to treatment with biomydin (aureomycin) and levomycetin (levorotatory chloramphenicol) given for 5 consecutive days. The first preparation is prescribed in doses of 0.3 g 4 times a day for the first 3 days and 0.3 g 3 times on each of the other two days; levomycetin dosages are 0.5 g 3-4 times a day.

### **Prophylaxis**

Prevention of Q fever is a difficult matter. Particular attention should be paid to disinfection of premises housing cattle and sheep. Special care must be taken during the calving and lambing season, when a great

quantity of the virus is shed not only with the milk and excreta of the animals, but with the amniotic fluid and placenta as well.

Q fever patients are hospitalised, their feces and urine are disinfected.

Milk delivered from infested farms may be used only after it has been boiled for no less than ten minutes. Pasteurisation does not sterilise this milk.

## PAPPATACI FEVER

---

Synonyms: mosquito fever, three-day fever, phlebotomus fever, summer "grippe", moskitka (Russian), hemp fever (in Italy), hava (local name); febris papatasii (Latin); pappataci (Italian); Pappataciefieber (German); fièvre de trois jours (French); fievre pappataci (Spanish); phlebotomus fever, sandfly fever, Chitral fever, three-day fever (English).

The term most commonly accepted is pappataci fever (although many English-speaking authors prefer phlebotomus or sandfly fever), after the Italian name of the phlebotomus vector, meaning to bite (pappo) silently or quietly (tace).

Pappataci fever is an infectious viral disease of hot climates that is transmitted from man to man by the bite of a sandfly.

### HISTORICAL DATA

Pappataci fever has evidently been known for a long time. It was first described under the name of "Mediterranean fever" by an English doctor, Barnett, on Malta in 1799. In 1804, Pim described an analogous disease — Gibraltar fever. Almost a hundred years later, in the summer of 1878, Dr. I.L. Yavorsky, participating in a Russian mission to Afghanistan, made a quite comprehensive and precise description of this fever in Mazar-i-Sharif. In 1886, Pick described pappataci fever as an independent nosologic unit. A report was published in 1905 by Taussig (Adriatic area) on the coincidence of pappataci fever and the habitat of the phlebotomus flies. This assumption was subsequently supported by Doerr (1909), who called the disease "sandfly fever" and proved in experiments on humans that it was transmitted by sandflies of the genus *Phlebotomus*.

The first cases of pappataci fever were described in 1917, in Tbilisi (then Tiflis), by Y. I. Martzinovsky and in the Crimea in 1923 by I. Y. Minkevich. N. I. Latyshev and I. N. Moskvina reported its incidence in



1924. Since 1925, the fever has been described and diagnosed in Tajikistan and Uzbekistan by S. V. Viskovsky, V. P. Petrov, G. A. Akovbyan, I. A. Kassirsky, and other authors.

### ETIOLOGY AND EPIDEMIOLOGY

The causative agent of pappataci fever is the filtrable virus *Febrigenes papatasi* (Doerr et al., 1909). Doerr, Frank, and Taussig (1909) succeeded in provoking pappataci fever in human beings in a non-endemic area (Vienna) by inoculating them with the blood of a pappataci patient passed through a Chamberland filter, as well as by exposure to the bite of phlebo-

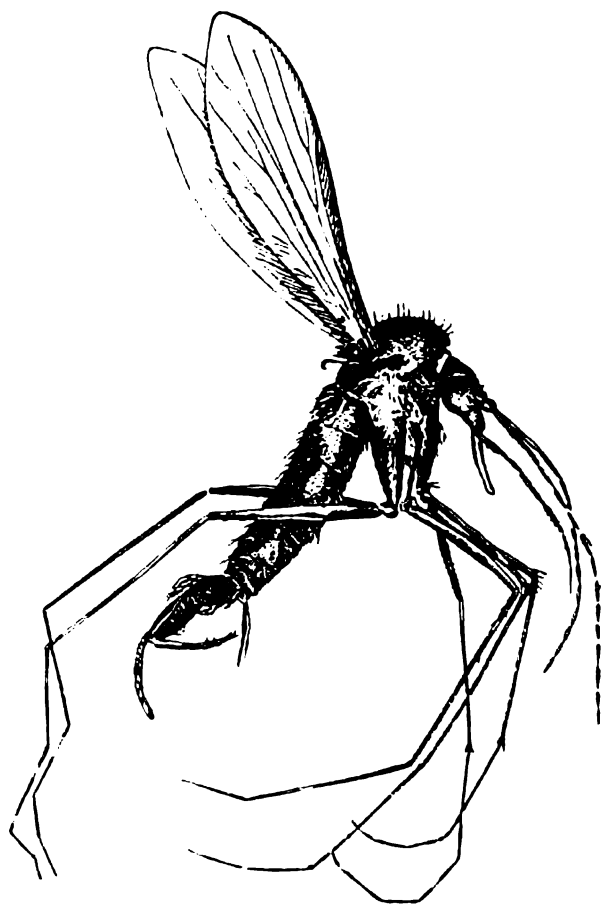


Fig. 116. *Phlebotomus papatasi*, vector of pappataci fever, male

tomus sandflies (Fig. 116) brought from Yugoslavia. In 1915, Birt succeeded in repeating Doerr's experiments by passing the infection through sandflies. In the U.S.S.R. A. I. Isaakyan obtained a positive result in one person out of three whom he had inoculated with a pappataci patient's serum passed through a Chamberland filter.

Three strains of the virus were obtained in experiments with volunteers, to whom the infection was passed from men who had served in the Mediterranean forces and had had pappataci fever (Sabin, 1943-45). Two strains from the Middle East and a third from Sicily proved to be identical. A fourth strain, from Naples, differed somewhat from the first three. Suboccipital inoculation is successful in rabbits (N. I. Khodukin and Y. Y. Sterngold) and in monkeys, but the course of the disease is a mild one. The pappataci virus is unstable, disintegrating at 55°C within several

minutes. Refrigerated blood serum retains its virulence for 3 to 5 months. The virus can be cultivated on the chorion-allantoic membrane (allantochorion) of the chick embryo, surviving several passages (N. I. Khodukin, 1943; N. A. Dyomina, 1941; M. N. Soshnikova, 1952). The human patient is the reservoir of the virus, although some data have been published concerning the presence of a reservoir among rodents. The transmission of the virus in sandflies by the transovarial route was proved by Soviet researchers (S. D. Moshkovsky, 1936; P. A. Petrishcheva, 1952). P. A. Petrishcheva continued these observations and demonstrated beyond doubt that the pappataci virus was transmitted from infested female phlebotomus flies to a third generation. Sandflies of the first generation that emerge from hibernating larvae become infestive only after their first ingestion of blood; the blood evidently activates the virus.

Six to eight days after a sandfly has ingested the blood of a pappataci patient it becomes capable of transmitting the infection to a healthy person. The pathogen is demonstrable in the blood one day before the onset of the disease and during the first two days of fever. Direct transmission of the infection is possible through a hypodermic needle or spring lancet in the absence of proper sterilisation.

The incidence of sandfly fever often assumes a mass scale. Outbreaks of this fever in hot lands are characterised by two waves corresponding to the swarming of phlebotomus broods. The first flight usually occurs in May and June, the second lasts from the end of July through August. Variations in the periods of epidemic outbreaks depend on the localities they take place in. In the Crimea and Northern Kirghizia only one epidemic wave is observed. In Tajikistan the present authors have observed a second outbreak in September.

A high incidence of pappataci fever is registered, for the most part, among non-immune newcomers in endemic areas. The local population acquires an immunity that is established in approximately 80 per cent of initial-infection patients. About 20 per cent of the inhabitants may contract the fever two and three times. Six to 12 per cent of repetition cases are possible during one epidemic season (S. V. Viskovsky, 1927; A. Y. Alymov, Y. S. Kon, 1954). Approximately 5 per cent of patients do not acquire immunity even after having had the fever twice.

### GEOGRAPHICAL DISTRIBUTION

Pappataci fever is a disease of countries with hot climates in *Phlebotomus*-inhabited areas, where the principal vector of the disease is *Ph. papatasi*. Consequently, in Europe, Asia, and Africa the disease is common to regions between 20° and 45° N. lat.

The fever is very widespread in Italy (northward, up to the valley of the Po), in Sicily, along the Adriatic coast, in Yugoslavia, Greece, on the islands of Malta, Crete and Cyprus, in Egypt and Syria, Jordan, Israel, Lebanon, Iraq, Iran, in the northwest and central provinces of India, in Southern China, a large part of Africa, in Central and South America.

Sandfly fever has not been registered in the U.S.A., although phlebotomus flies do live there (see above). In the U.S.S.R. the disease has been observed on the Crimean coast of the Azov and Black Seas, in the Uzbek, Turkmen, and Tajik Republics.

### CLINICAL ASPECTS

The incubation period of pappataci fever ranges from 3 to 7 days. The disease sets in suddenly with mild chills (occasionally without them), headache and severe muscular pains, particularly in the eyes and in the lumbar and gastrocnemius muscles. Movement of the eyeball is accompanied by acute pain. Occasionally pains are felt in the joints, as in dengue.

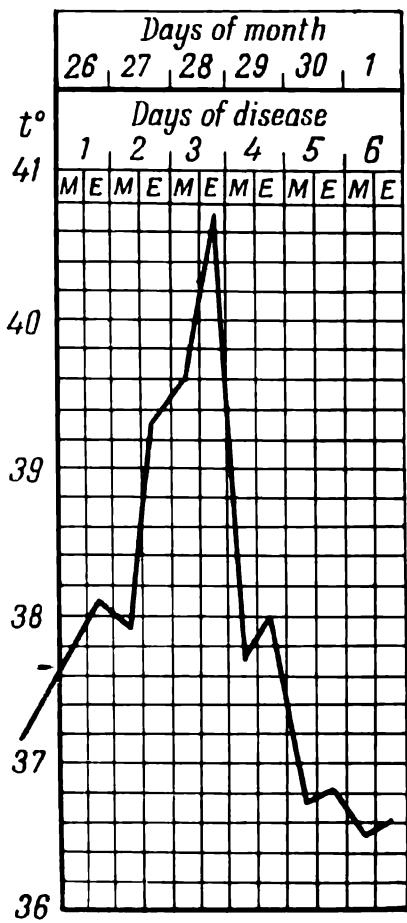


Fig. 117. Temperature curve in case of pappataci fever

The temperature soon rises to 39-40°, but for no longer than 2 to 4 days, terminating by a short crisis and falling below normal, at which level it stays for 2-5 days; this period is characterised by acute debility (Fig. 117). In some cases a critical decrease in temperature is noted. The pulse does not keep up with the fever, commonly attaining 90-95 beats per minute at 39-40°C. The heart sounds are dulled.

The signs most marked upon examination of the patient are a flushed and somewhat puffy face, coldsore (herpes labialis), and intensively injected scleral vessels, particularly at the outer corners of the eyes in the form of triangles the peaks of which point to the cornea (Pick's sign), densely white-coated tongue, hyperemia of the fauces, hyperemia and edema of the uvula with pin-point hemorrhages at its base; occasionally an ephemeral roseolous rash is seen (personal observations).

The authors have on several occasions seen a markedly expressed cutaneous eruption all over the body during an outbreak of pappataci fever in Tashkent; in some places this rash resembled measles. The rash erupted on the second or third day of the disease and persisted even after the temperature had fallen. A thorough investigation of the district showed the absence of dengue vectors (*Aedes*) and the presence of great masses of *Ph. papatasi*; this pointed to the presence of eruptive pappataci fever.

There are, as a rule, no catarrhal findings in the upper respiratory tract in cases of pappataci fever. The authors have occasionally noted a slight rhinitis, and also bronchitis; the same was observed by other authors during certain epidemics. In rare cases pappataci is accompanied, as in dengue, by nosebleed, bloody vomit, hemorrhage from the mouth, intestinal hemorrhages, etc. No enlargement of liver or spleen have been noted.

The gastroenteric symptoms described by some authors as being associated with pappataci fever (hence the term gastroenteritis climatica) are most probably exacerbations of some old intestinal disease (Y. S. Kon).

Blood counts show the presence of a moderate leukopenia with an eosinophilia and absolute lymphopenia on the first and second days of the disease; a stable neutropenia with increase of band cells develops during the subsequent days. Convalescence is marked by a rapid increase of the segmented neutrophils. The eosinophil count gradually returns to its normal values.

The differential white blood count becomes normal a week or two after recovery.

The prevalence of *nervous system* findings in the clinical pattern of sandfly fever is so pronounced that many authors hold that the pappataci virus is electively neurotropic. The most marked changes in the nervous system are a number of subjective and objective disturbances, intensive headache and muscular pain, meningeal symptoms with some serous exudation in the cerebral membranes, positive reactions to the Pandy and Nonne-Apelt tests, affection of the autonomic centres manifested by an unstable equilibrium of the parasympathetic and sympathetic nervous systems (bradycardia, red and white dermographism, positive Aschner phenomenon, brisk reaction of the pupils). The decrease in temperature is accompanied by a considerable decrease in the tonicity of the autonomic nervous system.

Delirium and loss of consciousness are occasionally observed. In severe forms of pappataci fever the patient remains in a state of complete prostration even after the fever has subsided, showing no conscious perception of his surroundings. The authors have seen such cases among physically well-developed servicemen affected with pappataci fever.

Mental depression, exhaustion, insomnia and muscular debility persist for a long time after the temperature has become normal. The cerebrospinal fluid is normalised by the 30th day following the onset of the disease (S. V. Viskovsky and V. P. Petrov, 1927).

The short (one-day) elevations of temperature 2-3 days following crisis that have been reported by a number of authors are very rare in Central Asia.

Prognosis is generally good. Mortality is practically non-existent. However, there was one outbreak in Ashkhabad (Y. S. Kon, 1954) of an extremely severe form of the disease, accompanied by hypertoxicosis and hemorrhagic symptoms. During this epidemic many fatal terminations were registered. Depression, general debility, and neuralgic pains may continue for quite a time after recovery.

## DIAGNOSIS

Pappataci fever differs from typhoid fever and paratyphoids by its fulminating onset, by the absence of splenomegaly, and by blood culture findings.

The onset of tick-borne relapsing fever may resemble that of pappataci fever, but the latter is again identified by the absence of splenomegaly, by the blood picture, and, what is most important, by the demonstration of spirochetes in relapsing fever and their absence in pappataci, and also by the different courses the two diseases take. As regards differential diagnosis between pappataci fever and malaria the enlargement and tenderness of the spleen in the latter disease must be borne in mind, as well as the type of temperature curve and the demonstration of plasmodia in the blood.

It is particularly difficult to differentiate pappataci fever from influenza. The latter may be negated by the finding of bradycardia, the occasional presence of cutaneous eruptions, the absence of catarrhal symptoms in the upper respiratory tract and uneventful recovery.

Signs speaking against dengue are the absence of the characteristic temperature curve, of the profuse and frequent rash, of changes in the joints, gait, etc. True, mild cases of dengue may sometimes follow a course identical to that of pappataci fever, making differential diagnosis exceedingly difficult.

## TREATMENT

No specific treatment is known. Therapy is reduced to symptomatic antidotes: in the presence of enteric stools a light protein diet is advisable, and calcium carbonicum and dermatol by mouth; enemas are recommended for constipation. Severe headache and muscular pains are alleviated by pyramidon, analgin (a Soviet analgesic), aspirin and other analgesics. Some authors recommend quinine as allegedly having a favourable effect on the course of pappataci fever. In cases of extreme restlessness sedatives and small doses of somnifacients (luminal, veronal, etc.) may be prescribed. It is highly important to explain to a patient frightened by the severity of the symptoms that the disease is neither dangerous nor of long duration. After the temperature subsides the patient is kept at bed-rest for several days, and in the subsequent two-three weeks quiet surroundings and limited mental efforts are recommended.

## PROPHYLAXIS

Extermination of sandflies and protection against their bites are the basic means of preventing pappataci fever.

*Antilarval measures.* Buildings should be cleaned thoroughly and all rubbish removed; this is both a general sanitary measure and a means of eradicating possible breeding places of sandflies. Rodent control is essential in combating these insects.

*Application of chemical agents to sandfly breeding places.* After all likely breeding places have been purged mechanically they are sprayed with a larvicidal preparation, a 20-30 per cent solution of calcium hypochlorite (5-15 litres per sq m) (Y. S. Kon and Y. K. Kachalova, 1952).

Probable breeding places should be sprayed with chemicals at regular intervals. Particular thoroughness is necessary in the April-May period in order to prevent the swarming of the first generation of sandflies and then in June-July to circumvent the second generation.

Of late the following larvicides have been proposed: naphthalene and vat residues of benzene polychlorines and paradichlorobenzene; however, all of them must still be tested in practice.

In Central Asia the sandflies mostly breed in the burrows of rodents (gerbils, gophers); the best method here is poisoning the burrows with chloropicrin.

*Sandfly extermination.* The measures that are carried out for the extermination of winged sandflies and for preventing these insects from molesting man are aimed first of all at protecting newcomers who have not had sandfly fever previously.

Particular stress is laid on control of sandflies in hospital wards and other premises housing pappataci patients (DDT and hexachlorocyclohexane [benzene hexachloride]).

*Preparations of stable action.* The best preparations for treating premises are DDT and benzene hexachloride which are strong contact poisons for sandflies.

The following preparations are at present available: dusts containing 5-10 per cent of pure DDT, kerosene emulsions containing 10-15 per cent of pure DDT, 10-25 per cent DDT turpentine emulsions, crystalline DDT, dusts containing 5-12 per cent of pure benzene hexachloride, turpentine emulsions with 10-15 per cent of pure benzene hexachloride, crystalline benzene hexachloride.

*Pyrethrum flowers.* Preparations of pyrethrum flowers are harmless for the higher animals and humans, but are highly toxic to insects. The active principle in pyrethrum flowers is pyrethrin, an insecticide that poisons insects upon direct contact. Pyrethrin preparations have no harmful effect on food, clothing, furniture and other domestic objects. No airtight sealing of premises is necessary. For ridding premises of sandflies 1-2 g of pyrethrum flower powder is applied per cubic metre of premises. The powder is diffused by means of special pulverisers.

*Flicid.* The most widespread of Soviet pyrethrum flowers preparations is flicid (called Flit in other countries), an infusion of pyrethrum flowers in benzene (gasoline).

*Pyrethrin candles* are smoking candles prepared with pyrethrum flowers; they burn slowly, emitting a smoke that has a highly toxic effect on sandflies and other insects.

*Soap-kerosene emulsions.* If preparations of stable action are not available then non-residential premises and, in some cases, living quarters as well, may be sprayed with a 3 per cent saponaceous emulsion prepared with naphtha, technical, green, or household soap.

*Sticky paper.* Sticky paper is hung in the corners of the rooms near the ceiling, where the insects usually keep themselves. As it dries, the paper is replaced by fresh paper (once in six days).

*Insect repellents.* For individual and group protection of people against sandflies various repellent agents are used.

These insectifuges are either applied to the open parts of the body, or are used for impregnating clothing, bedding and bed-nets.

The most widely used insect repellents applied to the open surfaces of the body are kerosene and, less frequently, oily salves. Their action is short (2-3 hours). Frequent application of kerosene to the skin may cause dermatitis. The following mixtures yield good results against sandflies (Y. S. Kon and Y. K. Kachalova): a) a mixture containing 8 parts vaseline, 2 parts citronella oil, 1 part camphor spirit and 1 part cedar oil, and b) a mixture consisting of anise oil, eucalyptus oil, and rectified turpentine (3 drops of each) in 30 g of lanolin. These mixtures, when rubbed into the skin, provide protection against sandflies for 1-1½ hours. In hot lands, where a great part of the people habitually sleep in the open air in the summer, it is recommended to impregnate the bed-clothes with a 5 per cent aqueous solution of K soap (K soap is a mixture of equal parts of household soap and K preparation, bis-ethyl-xanthogen  $C_2S_4O_2[C_2H_5]_2$ ). A new synthetic preparation has lately been proposed, dimethyl phthalate, a pleasant-smelling oily liquid. It is either rubbed slightly into the skin, or applied to clothing. The preparation (20 to 30 g) is applied to the open parts of the body. The duration of the repellent effect is 3 to 4 hours.

*Mechanical protection.* Mechanical measures of protection against insects (screens on windows and doors, bed-nets) are successful only if observed with utmost care. Bed-nets should be available at all pharmacies.

The windows and doors of private dwellings, hospitals, children's institutions, etc., should be screened with gauze or metal meshes with openings no larger than 1 mm.

Bed-nets are not always effective in the presence of large numbers of insects. It is therefore recommended to impregnate the nets with aqueous suspensions of DDT or benzene hexachloride.

If these preparations are unavailable the nets may be treated with a 5 per cent water-and-kerosene emulsion or with a 2 per cent emulsion of K soap.

Fans should be used extensively in premises where night work is in progress: strong currents of air repel the sandflies.

# DENGUE

---

Synonyms: dengue (Lat., Engl. Germ., Fr., Sp.); dandy fever, dengue f., breakbone f. (Engl.); denghero (Ital.); breakbone fever, joint f., giraffe fever, five-day fever, seven-day fever (Russ.), date disease (in Egypt).

Dengue is an acute febrile disease of the tropics and subtropics characterised by severe pain in the bones and muscles; it is transmitted by *Aedes* mosquitoes.

## HISTORICAL DATA

The first report on dengue was made by Bilone who described it as “joint fever” in 1779 in Batavia, on the island of Java. A year later Benjamin Rush described an epidemic of dengue in Philadelphia. Numerous heavy epidemics in the tropics and subtropics were described in the 19th and 20th centuries.

The London Royal College of Physicians gave the disease the name it now bears—dengue.

According to the data published by Sabin (1946) the greatest dengue epidemics occurred after 1920. In 1922, five to six hundred thousand cases were registered in Texas (Chandler and Rice); from 1 to 2 million people had dengue in the southern states of the USA in 1935 (Siler); the epidemic of 1925-26 in Queensland and New South Wales affected close to 560 thousand people (McCallum and Dwyer); outbreaks of dengue occur every year in Greece, but a heavy epidemic was noted in 1927-28, when the total incidence exceeded 1 million.

Large dengue epidemics (1-2 million people) took place in the southern seaports of Japan (Osaka, Kyoto, Nagoya, and others).

The idea that *Aedes aegypti* was the vector of dengue was first conceived in 1906. This assumption was subsequently confirmed. The viral nature of the disease was established in 1907 by Ashburn and Craig; in the years 1929-31 Blanc, Caminopetros, Simmons and others discovered the infec-



tion among certain species of monkeys, thus revealing a natural reservoir of the disease.

Sabin (1944) made a most detailed study of the dengue virus, in the course of which he established a number of immunological types.

### ETIOLOGY AND EPIDEMIOLOGY

The etiologic agent of dengue is the virus *Viscerophilus dengue* (Ashburn a. Craig, 1907), which can grow on a chorio-allantoic membrane. The genesis of the dengue virus is still a moot problem. Some resemblance to the viruses of yellow fever, West Nile fever, Japanese encephalitis and St. Louis encephalitis (Sabin) has been noted, but they are not identical. For instance, volunteers immunised to the 17-D strain of the yellow fever virus proved non-resistant to small amounts of the dengue virus. The latter is not very stable in the laboratory, keeping no longer than 3 weeks; it disintegrates at 50 °C, is rapidly destroyed by desiccation, but is very stable in serum: frozen, it is preserved at minus 70 °C, when desiccated and kept at 5 °C, its virulence is preserved for 5 years (Sabin).

Certain strains of the virus are transmissible to mice, and they may be maintained in serial passages by intracerebral inoculation. In rhesus macaques the intracerebral inoculation of dengue virus adapted to mice results in a morbid condition characterised by fever and occasionally by mild paralyses of the extremities and lethal termination (in the latter cases the histopathologic findings are similar to those observed in experimental poliomyelitis).

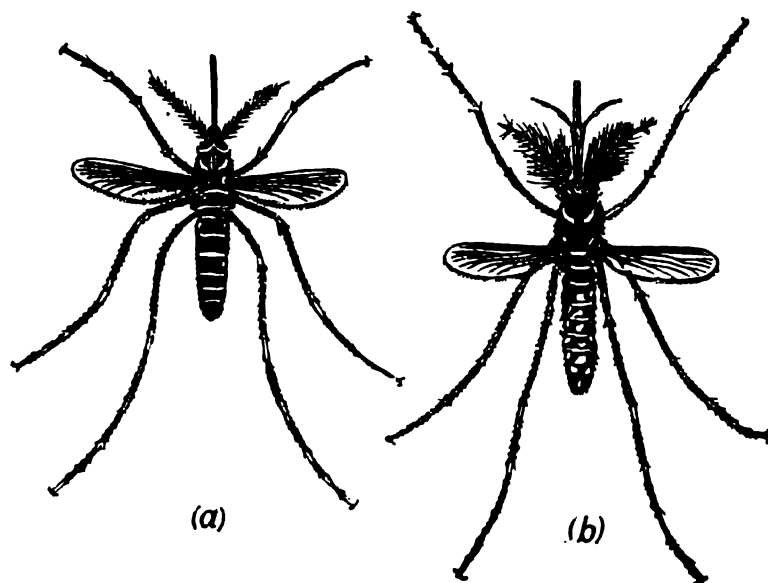


Fig. 118. *Aedes aegypti*, vectors of dengue  
a – female; b – male

The viral nature of dengue has been confirmed experimentally by inoculating volunteers with the virus after it has been passed through mice and monkeys. It was established at the same time that *Aedes aegypti* mosquitoes (Fig. 118) that ingest the blood of human dengue patients and infected mice, are capable of transmitting the infection to other people through their bites. However, after the 7th passage on mice the

Hawaiian strain of the virus no longer causes severe morbidity and typical fever in human beings; instead, it evokes a rash and a stable immunity to the unchanged virus (Sabin).

The vector of dengue is the mosquito *Aedes aegypti* (L.) (synonyms: *Stegomyia fasciata*, *Stegomyia calopus*), and also *Aedes albopictus* (Skuse) and *Aedes scutellaris* (*Aedes hebrideus*) (Walk). The *Aedes* mosquitoes belong to the family *Culicidae*. *Aedes aegypti* is a small mosquito with a lyre-like pattern on its back, a silvery colouring of the proximal sections of each leg, and silvery spots on the lateral lines of the abdomen.

*Aedes* (*Stegomyia*) *aegypti* (*stegomyia* means "living at home") is basically a domestic and yard mosquito. Its first attack on man during its first flight takes place in the daytime, but thereafter its bloodsucking activities are carried on at night. *A. aegypti* is sensitive to oscillations of the atmospheric temperature; it perishes in the summer at temperatures lower than 15-10 °C.

The mosquito may acquire the infection 6-8 hours prior to the onset of the disease in its victim, and during the first three days after the beginning of the disease. A certain period is needed for the mosquito to become infective (the so-called "external" incubation period during which the virus becomes active in the body of the mosquito), that lasts from 8 to 14 days. Under optimal conditions the mosquito becomes infective 8-14 days after ingesting infected blood and retains this capability throughout its life, i.e., from 1 to 3-4 months.

The principal reservoir of the infection are sick people, particularly in localities where the vector is *Aedes aegypti*, the bloodsucking mosquito that molests man; however, in the jungles and scrub areas of a number of tropical lands *Aedes albopictus* prevails. The latter feeds on monkeys, spreading the infection among them (jungle dengue epidemics).

## GEOGRAPHICAL DISTRIBUTION

Dengue is most widespread in the tropical and subtropical belt of North Central, and South America (where the vector of the disease *Aedes aegypti* is common), in the southern states of the U.S.A. (Texas, New Mexico, Arizona, California, Florida, etc.), in the central part of the American continent (Mexico, Honduras, Costa Rica, Panama, etc.), and also on the Caribbean islands, in Brazil, in the basin of the Coral Sea (the New Hebrides), in Queensland (Australia), Indonesia, the southern seaports of Japan, on the Philippines, in India, Egypt and Syria, Sudan, Lebanon, Saudi Arabia, Greece, on Cyprus, in Southern Spain. In the U.S.S.R. dengue has not been registered.

## CLINICAL ASPECTS

The incubation period of dengue lasts from 3 to 14 days, 5-8 days on the average.

There are usually no noticeable prodromal signs. The disease sets in suddenly with a high temperature (39-41°). The fever usually persists for

5-7 days, with characteristic drops on the 2nd or 3rd day (the fall is critical, accompanied by profuse sweating) (Fig. 119). The pulse is 120 beats per minute. Patients complain of chills during the febrile stage. The chills are accompanied by severe headache, particularly in the back of the head, pains in the eyes, in the spinal muscles, in the joints. The muscular and joint pains may become so severe that the patient is afraid of moving, becoming particularly careful about the larger joints and the spinal column.

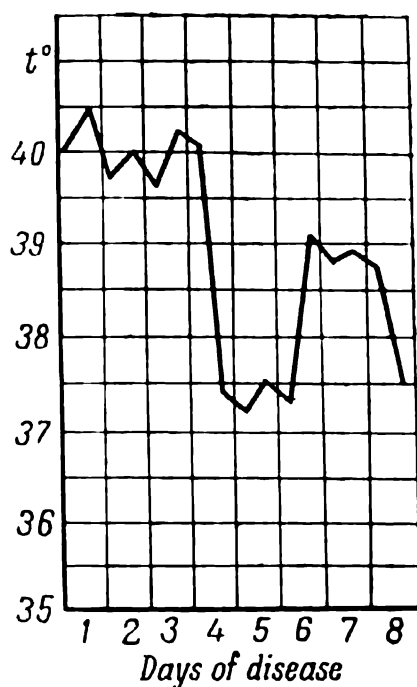


Fig. 119. Temperature curve in dengue

He lies in bed stretched out to his full length, and if he does get to his feet his gait is extremely stiff. This latter is considered to be responsible for the name dengue—distorted “dandy”. Another figurative name of the disease, giraffe fever, also stresses this peculiarity in the clinical status of the patients. The appearance of the patient is also characteristic—a flaming red face, the cheeks and, especially, the forehead are hyperemic, the conjunctivas are acutely injected, the eyes bright; a scarlatinous redness of the entire body is not uncommon. The general toxicosis is very great, causing nausea, vomiting and complete loss of appetite throughout the period of the disease. The tongue is furry and swollen.

On the second or third day a pin-point rash erupts, principally on the elbows and knees; on the third to fifth day a maculopapular rash resembling measles or a scarlatinous rash erupts, first on the chest, back and abdomen, then on the extremities and face. However, it is only in 70 per cent of cases that a well-developed rash is observed. In some places these eruptions are tiny petechial spots covering the posterior aspects of the legs, feet, hands, the buccal mucosa and soft palate. The rash usually disappears with defervescence, or it may continue for a day or two after the crisis. After the rash pales scaling is observed, commonly for several days (Fig. 120). The lymph nodes are usually enlarged and tender; the liver is slightly enlarged, while the spleen is not. Blood findings are a normal white blood count with a moderate neutrophilosis, followed by

leukopenia with relative and absolute lymphocytosis after the third or fourth day of the disease. A moderate eosinophilia is noted in the concluding stages of the disease.

*Complications* (prolonged subfebrile conditions after recovery, hemorrhagic diathesis) are very rare.

## DIAGNOSIS

In epidemic areas it is important to establish, besides the clinical diagnosis, a virological diagnosis for precise identification of dengue, so that timely prophylactic measures can be taken against its diffusion.

For isolating the strain of the virus the blood specimen is taken from the patient 24 to 48 hours after the onset of the disease. Ordinarily mice sucklings no older than 3 days are inoculated; however some authors have inoculated human volunteers. Recovery of the virus is authentic if the characteristic features of dengue are reproduced, after an incubation period of 5 days, in a volunteer who has been exposed to the bites of *Aedes aegypti* mosquitoes in the bodies of which the infection has passed the necessary "external" incubation period. The strain recovered from mice is identified as follows:

- 1) by its pathogenicity in relation to certain animals (mice, monkeys);
- 2) by neutralisation with serums containing only the specific dengue antibodies obtained from Rhesus macaques;
- 3) by infecting mice and, a month later, testing their immunity to 100 LD<sub>50</sub> of known strains of a powerful virus adapted to mice. Of recent years the complement-fixation reaction has been introduced for serologic diagnosis.

## DIFFERENTIAL DIAGNOSIS

There is a close resemblance to pappataci fever (in the general status of the patient, his temperature curve, the seasonal appearance of the disease), epidemics of which are not infrequent in the same localities as dengue. However, dengue is distinguishable from pappataci fever by the presence of a rash and marked arthritic symptoms.

Dengue differs from influenza by the absence of catarrhal symptoms in the upper respiratory tract and by its seasonal occurrence associated with the swarming of the mosquito vectors.

Dengue may frequently imitate measles; however, it differs from the latter by its sudden onset, absence of catarrh of the mucous membranes of the respiratory passages and absence of the Filatov-Koplik spots.

The appearance of a rubella-like rash may lead to the confusion of dengue with rubella (German measles); however, dengue is differentiated by the absence of pharyngitis and enlargement of the occipital lymph nodes so typical of rubella. A scarlatinous rash, pruritus and scaly desquamation may lead to the assumption of scarlet fever, but it must be borne in mind that in dengue no bright, clearly contoured inflammatory area is observed in the throat and, besides, the blood pattern is different:

scarlet fever is characterised by an increasing neutrophil leukocytosis, while the opposite—increasing leukopenia with neutropenia—is observed in dengue.

### PROGNOSIS

Prognosis is almost always favourable for dengue. It is only in extremely severe hypertoxic forms and in very weak patients that fatal terminations occur (the mortality rate among such patients, whose condition is due to alimentary dystrophy and advanced age, is 0.1-0.2 per cent).

Defervescence is followed by a convalescent period of a week or two, during which the patient slowly recovers from the adynamia and neurasthenia caused by dengue.

### PATHOLOGY

Although post-mortem material is relatively limited, the following findings have been reported: degenerative changes in the liver, kidneys, heart, and brain, hemorrhages in the endocardium, pericardium, pleura, gastrointestinal mucosa and nervous system. Particularly marked lesions are observed in the vascular system at the eruptive sites: swelling of the endothelium, perivascular edema, and infiltration of cells with rounded nuclei.

### TREATMENT

The treatment of dengue is restricted to symptomatic therapy, as no specific agents are known. Bromides and barbiturates are recommended for the general symptoms associated with the overstimulation of the nervous system caused by the infection. Pyramidon and analgin are recommended as anodynes for pains in the joints and muscles. Cardiac weakness is treated with cardiac agents and intravenous infusions of glucose.

### PROPHYLAXIS

Dengue control can only be effected by mass extermination of *Aedes* mosquitoes in their breeding places, particularly in populated communities. Emphasis should be laid on mosquito extermination in the premises of railroad stations, airports, sea- and river-ports and adjacent areas, aboard ships and in planes. The best exterminatory agent is DDT. Screens should also be installed, and bed-nets used at night.

## YELLOW FEVER

---

Synonyms: febris flava, febris biliosa, typhus icteroides (Lat.); Gelbfieber (Germ.); fièvre jaune (Fr.); fiebre amarilla, vomito negro (black vomit) (Span.); virus amaryl or "Amaryl" (Intern. nomencl.).

Yellow fever is an acute transmissible infection caused by a filtrable virus; it is characterised by jaundice, hemorrhagic diathesis and nephropathy; the mortality rate is high.

### HISTORICAL DATA

Yellow fever was first reported on soon after the discovery of America. A definite epidemic of yellow fever was described in Yucatan in 1648, and then in 1694 in Central America, by Tereira da Ros.

Heavy epidemics of the disease were subsequently described in the 17th, 18th, and 19th centuries, and in the 1920's. These epidemics broke out in Baltimore, Philadelphia, New York, Central America, the Caribbean basin, Brazil.

Up to 500 thousand people were sick with yellow fever in the U.S.A. in the years between 1793 and 1900. In Spain 60 thousand people died of yellow fever in 1800; in Havana (Cuba) epidemics of varying severity occurred between the beginning of the registration of yellow fever (1649) and 1900 and up to 35,900 fatal cases were registered between the years 1803 and 1900. In Brazil (Rio de Janeiro, São Paulo) and Central America hundreds of thousands of people had yellow fever in the 19th century, of them approximately ten thousand died during the construction of the Panama Canal.

A point worth mentioning is the fact that although there had never been any yellow fever in Russia Russian researchers followed the development of epidemics in foreign countries with close attention. When an epidemic of yellow fever broke out in 1805 in Spain and in the south of France the Medical Council in Petersburg published *A Description of*

*Yellow Fever Presenting Attacks, Causes and Methods of Treatment and Prevention* (cited from V. S. Suvorov, 1957), a paper that still retains its value. According to V. S. Suvorov the unknown author of this *Description of Yellow Fever* queried, 43 years before Nottom (1843) and 76 years before Findley (1881), whether "... insects were perhaps conducive to its dissemination."

A book published in 1806 by a Russian army doctor F. Korsh, also called *Description of Yellow Fever* sets forth highly interesting concrete prophylactic measures against the endemic introduction of yellow fever to Russia.

A prominent part in bringing yellow fever under control in America, particularly on Cuba, was played by Reed, Gorgas and Carter. In 1901, while working in Havana, Walter Reed established that the yellow fever virus passed through filters that did not let bacteria through. At that same time it was firmly established that the *Aedes aegypti* were responsible for the transmission of yellow fever (Reed, 1911; Carter, 1931). Measures undertaken for gaining control of the mosquito in populated communities, particularly in the principal site of yellow fever, Guayaquil (Ecuador), led to the extermination of the disease on the Pacific coast of South America; however, in 1928 a severe epidemic suddenly broke out in Rio de Janeiro. In Africa it was established during this period that Rhesus macaques were susceptible to the yellow fever virus. Experimentally the disease was transmitted through mosquitoes of other species, while in a number of areas of South America (the jungles) and in Africa natural foci of yellow fever were discovered in areas where there were neither *Aedes aegypti* nor man (human beings were only affected subsequently, when they appeared in the jungles).

Thus a new form of yellow fever was discovered — jungle yellow fever — a form that occurs in or near forested areas where the *Aedes aegypti* has not been found; wild mammals of the jungles are the reservoir of the virus of this infection.

## ETIOLOGY

The causative agent of yellow fever is a filtrable virus, *Viscerophilus tropicus* (Reed a. Carrol, 1911) measuring 18-27 millimicrons. It forms into inclusions located in the nuclei of the liver cells(?).

Modern knowledge on the etiology and epidemiology of yellow fever is principally associated with the works of a commission headed by Walter Reed (1911); it was established by this commission that the yellow fever agent passes through bacterial filters, that it is present in the patient's blood during the first three days after the onset of the disease, that the vectors of the disease are the *Aedes aegypti* mosquitoes, and that the bite of these mosquitoes is infestive if no less than 12 days have elapsed after the mosquito has bitten a yellow fever patient and ingested his blood.

The Anglo-American and French commissions that worked in West Africa in 1926-28 presented the final proofs of the viral nature of yellow fever.

The yellow fever virus is very susceptible to physical and chemical factors, therefore a 5-10 per cent solution of serum must be added when working with it. The virus is preserved several months in 50 per cent glycerin. The best way of preserving the virus for a prolonged period (a year and longer) is by lyophilisation (rapid freezing and dehydration). The virus retains its vitality for 3 days in the dead bodies of infected mosquitoes at 26-27 °C, and for over a month at the freezing point (approximately).

The viral strains exist in pantropic forms (affecting all organs and tissues) and in neurotropic forms. By means of serial intracerebral passage in mice the natural virus is transformed into a fixed neurotropic strain, which, however, retains the capacity to confer immunity against infection by the natural virus. Extreme caution is necessary in handling the blood of yellow fever patients in the laboratory and during post-mortem examinations; contamination of the blood or mucous membranes of healthy people with infinitesimal quantities of infected matter is enough for the reproduction of the infection in these people.

The yellow fever virus grows in chick embryo tissue cultures and multiplies upon inoculation into mice testicles; this method is the basic principle underlying the serial production of the virus. A mildly virulent strain is obtained by cultivation of the virus on chick embryo membranes; one of these strains, 17-D, is employed for vaccination.

Recently the complement-fixation and neutralisation tests have been introduced into practice for diagnostic purposes. Great practical value is attached to the neutralisation test, as the neutralisation reaction is retained for a long time in the blood of people who have recovered from yellow fever. Mice are highly susceptible to the yellow fever virus (intracerebral inoculation); the same is true of monkeys. In nature the most susceptible animals are monkeys, the European hedgehog, marsupials, the peccary, and some others.

### EPIDEMIOLOGY

The principal vector of yellow fever is the *Aedes aegypti* mosquito. Only the females contract the infection and transmit it, as blood-feeding following fertilisation is obligatory for the development of the ova and for oviposition. The virus is demonstrable in the blood of yellow fever patients and is passed to the mosquito vectors towards the end of the incubation period and during the first three days of the disease.

The possibility of direct transmission of the infection by contamination of a superficial skin lesion or the mucous membranes with insignificant amounts of blood has been pointed out (whilst taking blood from a patient, or performing an autopsy).

The mosquitoes become infective to man only some time after ingestion of infested blood. At higher temperatures this period is shorter: at 18 °C it is 30 days, at 21° 18 days, at 31° 6 days. The mosquito remains infective throughout the rest of its life.

The *Aedes* mosquitoes are not particular in selecting a place for oviposition. They lay their eggs in hollow trees, in any puddle contaminated



with organic matter, in glass vessels containing dirty water, in garbage dumps, etc.

In the tropics *Aedes aegypti* multiplies and blood-feeds the year round; thus transmission of the infection is possible in the tropics throughout the year. On the northern frontiers of the distribution of yellow fever (32-38°N. lat.) the *Aedes* winters in the ova stage. Transmission of the infection is here possible before the onset of cold weather in the autumn.

That mosquitoes are vectors of yellow fever was proved experimentally by infecting *Aedes aegypti* with the virus and then transmitting it through the bites of these mosquitoes to Rhesus macaques, white mice, hedgehogs, and other animals in whom yellow fever was successfully reproduced. Doctors Walter Reed and Jesse Lazear both lost their lives when they tested on themselves whether *Aedes aegypti* was the vector of yellow fever.

Two epidemiologic types of yellow fever have been established: the urban and jungle types. The first is observed in cities and large populated communities. Its transmission cycle is man—*Aedes aegypti*—man. Consequently, man is, like the mosquito, also a reservoir of the virus.

In the jungle thickets, where there are neither man nor *Aedes aegypti*, another epidemiological form of yellow fever exists; the reservoir of the jungle yellow fever virus are other species of mosquitoes and various wild animals—monkeys, marsupials, armadillos, ant-eaters, hedgehogs, certain rodent species.

In Africa, where the *Aedes aegypti* is most widespread, the urban type of yellow fever prevails (particularly on the Western Coast and in Central Africa), in South America both types are observed. It has now been established that both viruses are identical.

Other vectors of yellow fever, besides *Aedes aegypti*, are: *Aedes geniculatus* (a species also encountered in the U.S.S.R.), *A. africanus*, *A. simpsoni*, *A. vittatus*, *A. scapularis*, *A. fluviatilis*, *Haemagogus spegazzini*, *H. equinus*, *H. carpicornii* (South American jungles), and other species.

In urban communities the disease usually appeared as a heavy epidemic that rapidly spreads from one community to another. The disappearance of yellow fever as a result of systematic extermination of mosquitoes has led to the conclusion that the cycle man—mosquito—man in urban conditions is the only means by which the infection is maintained. Since approximately 1924 no yellow fever has been registered in Central America (the Panama Canal and the basin of the Caribbean Sea; the last epidemic north of the Panama Canal occurred in 1924 in Salvador).

In Africa, where conditions for extermination of *Aedes* mosquitoes are less favourable as the breeding habits of the mosquito are not so urban, and where there are no water mains, etc., epidemics are still frequent.

Evidently, the vector of the infection is not *Aedes africanus* that lives in forested areas, but *Aedes simpsoni*, a mosquito habitating plantations (the tubular bases of leaves). Foraging monkeys transmit the infection to the mosquitoes, the latter pass it on to man.

Jungle yellow fever occurs in South America in epidemic and endemic forms (the latter annually). It principally affects adult males who contract it while working on the land.

The virus of yellow fever is maintained in this belt by various wild mammals (insectivorous animals, Edentata, rodents, monkeys), and its vectors are *Haemagogus spegazzini*, *H. equinus* and other mosquitoes. Besides the endemic form there is also an epidemic form of yellow fever in the jungles. Jungle yellow fever is transmitted by people who work in the forests to distant settlements in the form of epidemics. The most severe of these was observed in the years 1933-38. The epidemic first broke out in the basin of the Amazon river, from where it spread southward through Brazil. The wave of the disease got to Rio de Janeiro and thence to areas more northerly.

GEOGRAPHICAL DISTRIBUTION

The area of yellow fever epidemics includes the tropical regions of South America and West Africa; however, epidemics have broken out in almost all tropical and subtropical belts of the Eastern and Western hemispheres inhabited by vectors of the disease (42° N. lat. and 40° S. lat.) owing to ecdemic transmission through sick people and/or infested mosquitoes.

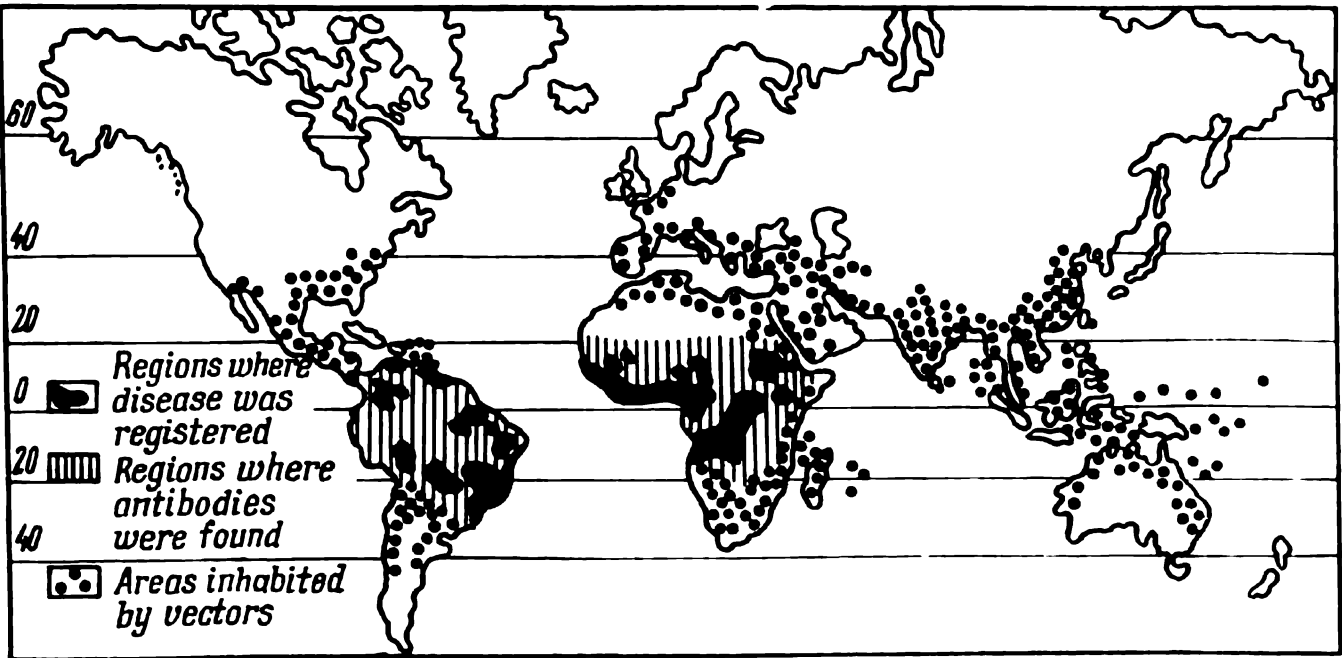


Fig. 121. Geographical distribution of yellow fever according to the data of the World Health Organisation (1933-44)

The development of the virus of yellow fever in the body of the mosquito apparently requires an optimal temperature no lower than 25-30°C; this explains the absence of yellow fever in more temperate climates, even though the mosquito vectors are present.

Evidently, yellow fever developed as a natural endemic disease of wild animals long before the advent of man (O. V. Baroyan and I. T.

Lozinskaya). The development of human society promoted the evolution of yellow fever into an anthropophilic infection as the result of the adaptation of the *Aedes* mosquitoes to human habitations.

At present yellow fever is common to the jungles of West, Central, and East Africa and South America (Brazil, British and French Guiana, Venezuela, Colombia, Ecuador, Panama, Nicaragua, Costa Rica, Peru, Bolivia, the Caribbean islands, the north-eastern part of Argentina (Fig.121). The total number of deaths caused by yellow fever is, according to registered epidemics, over 3 million.

Epidemics of yellow fever may appear at great distances from the basic sites of the disease in the presence of mosquito vectors and a suitable atmospheric temperature following epidemic introduction.

Thus, yellow fever was not infrequently brought into southern Europe, resulting in severe epidemics in Spain and Portugal. During the great epidemic of 1857, 19 thousand people were taken sick in Lisbon, 7 thousand of them died. In 1870, an epidemic broke out in Barcelona; from there the infection spread to the southern parts of France and Italy.

No cases of yellow fever have been registered in the Soviet Union.

The development of international air and water communications increase the danger of transportation of infested mosquitoes, as the latter may settle in ships or planes.

The short time now required to cover great distances by plane makes it possible for people arriving from other lands to be in the incubation phase of the disease, or to have contracted it on the way.

## CLINICAL ASPECTS

Yellow fever is usually a severe disease, but in a certain percentage of cases it appears in a mild form. The incubation period varies from 3 to 9 days. In typical cases the disease is divided into two phases with a short period of remission between them.

*First phase.* The disease usually sets in with severe chills followed by an elevation of the temperature to 39-40°C. The fever remains at this level for 3-4 days, and then falls to 37-38°. The pulse is accelerated to 120-130 beats per minute. Patients complain of severe headache, pain in the epigastric region, the spinal muscles and lower extremities. They are extremely excited and restless, toss about in their beds, and are afflicted with photophobia. In severe cases delirium appears. The tongue is white-coated on the dorsum and red at the edges and point. In severe cases the lips and mouth are coated with a fuliginous (soot-like) film. Severe nausea and vomiting appear at the very beginning of the disease. The spleen and liver are slightly enlarged and tender to palpation. Symptoms of infectious albuminuria are noted (Fig. 122).

At this phase of the disease the face of the patient has a quite characteristic look: it is flushed and swollen, the eyes are shining and blood-shot (*the amaryl mask*).

*Second phase.* The disease passes into its second phase on the 4th or 5th day after a short remission of fever (for 12 to 24 hours). This second phase is marked by the appearance of jaundice, hemorrhagic diathesis and uremia. An early sign of coming jaundice is the change from tachycardia to bradycardia (the pulse goes down to 60 beats per minute). The temperature becomes hyperpyrexial (40-41°C), remaining so for another 4 or 5 days, after which it resolves by crisis.

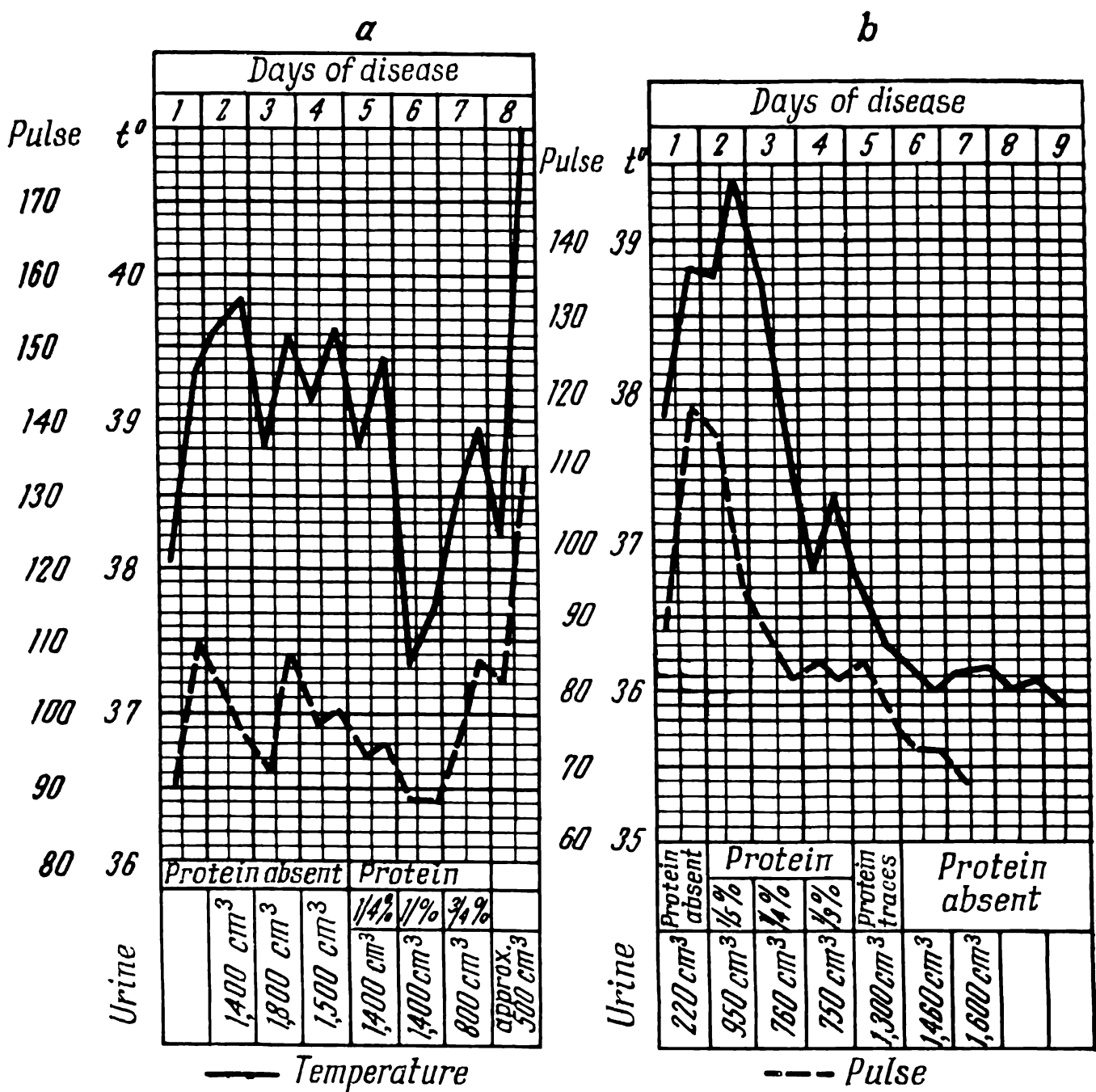


Fig. 122. Temperature curves, pulse rates, and protein values in urine of yellow fever patients:  
*a* – fatal case; *b* – mild form

By the eighth or ninth day of the disease the jaundice becomes very intensive, the skin acquires a reddish-brown tinge, albuminuria and hematuria increase, residual nitrogen in the blood attains high values. The gums bleed, nosebleed and intestinal hemorrhages appear, as well as hemorrhagic spots on the skin against a polymorphous rash. Black vomit is often observed (the colour of coffee dregs).

Frequent nervous system findings are toxic encephalitis; the blood shows a neutrophilic leukocytosis and aneosinophilia; in the serum both the direct and indirect reactions to bilirubin are obtained, in the urine bilirubin and an increased urobilin content are noted. The feces are coloured.

Two forms of the disease are distinguished: the *severe form* just described, and the *mild form* in which the temperature is elevated for no longer than 4-5 days, the jaundice is not severe, and no hemorrhagic complications occur. Sometimes mild forms of yellow fever are mistaken for other diseases—influenza, infectious hepatitis (Botkin's disease).

## DIAGNOSIS

*Differential diagnosis.* Yellow fever may be confused with many diseases: tropical malaria (the biliary form), Botkin's disease (infectious hepatitis), spirochetal jaundice (disease of Weil and Vasilyev), malarial hemoglobinuria and other acute hemolytic jaundices associated with intravascular hemolysis.

Differentiation between malaria and yellow fever is established by epidemiologic data, the presence of plasmodia in the blood, and the enlargement of the spleen and liver.

The onset of infectious hepatitis (Botkin's disease) is commonly not as severe as the onset of yellow fever, the feces are discoloured and no hemorrhages are noted.

Spirochetal jaundice is very like yellow fever, but it differs from the latter by its longer febrile period, absence of black vomit, and by the development of characteristic complications (pericarditis, meningitis). Leptospire are demonstrable in the urine of spirochetal jaundice patients; the agglutination reaction with the leptospire is positive.

Malarial hemoglobinuria and other hemolytic conditions with intravascular hemolysis are distinguished from similar conditions due to yellow fever by definite anamnestic data (malaria treated with quinine preparations; effect of toxic preparations and allergic factors in other acute hemolytic conditions) and the sudden onset of the disease with the appearance of "black urine".

Differentiation between yellow fever and pappataci and dengue is somewhat difficult at the beginning of the disease; however, jaundice is absent in the latter diseases, no renal symptoms are observed, the blood count shows leukopenia, and the general course is more benign.

In difficult cases yellow fever is diagnosed in the laboratory by special virological and serological tests, or by recovering the virus after intracerebral inoculation of monkeys or white mice with whole blood or serum.

The method most widely used in diagnosis is the reaction of neutralisation by which an increased antibody content in the patient's blood is evaluated. Two specimens of serum are taken, the first at the very beginning of the disease, the second upon recovery.

A mixture of serum and the virus are injected into the brains of mice. If there are no, or very little, antibodies in the first specimen, while the second prevents the death of the mice, it may be concluded that the patient has just recovered from yellow fever; if both specimens contain an equal amount of the antibodies it may be assumed that he has had the disease in the past.

### PROGNOSIS

Prognosis is poor for the severe form of yellow fever; in 60 per cent of cases its termination is fatal; people of advanced age particularly tend to succumb to it. In less severe epidemics the mortality rate is 5 to 10 per cent. Mortality among children is generally low (3-5 per cent).

### PATHOLOGY

Macroscopic changes: icteroid and purplish-red integuments (the latter due to venous hyperemia). The liver is slightly enlarged, somewhat yellowish, section shows fatty degeneration. The kidneys are also yellowish, enlarged, with signs of fatty degeneration; hemorrhages are apparent on the gastric mucosa.

Microscopic changes: most characteristic are lesions of the liver — hemorrhages, cloudy swelling, fat necrosis of the cells (the location of the necrotic elements in the lobules is principally a central one, but in severe cases the entire lobule is involved). The necrotic lesions are characterised by hyaline impregnation of a part of the cytoplasm (Councilman necrotic hyaline bodies). The Kupffer cells are enlarged, granulated.

Regenerative cellular restoration of the liver occurs during convalescence. Swelling and fatty degeneration of the convoluted tubules are apparent in the kidneys. The spleen is intensively filled with blood and infiltrated with leukocytes; signs of degeneration and necrosis in the Malpighian corpuscles (lymph nodules) are the proliferation of large reticular monocytes. Cardiac lesions: degeneration of the cardiac muscles.

Encephalitis is manifested in man and in monkeys by necrosis of the ganglial cells and perivascular infiltration.

In severe cases (chiefly artificially produced) the cells of the liver and of other viscera are seen to contain irregular, unequal, acidophilic granules—inclusion bodies which stain with fuchsin-methylene blue. These bodies are arranged in the nucleus around the nucleolus.

### PATHOGENESIS

The virus of yellow fever spreads from the site of inoculation (after the bite) to the regional lymph node, where it multiplies; thence it spreads with the blood stream and affects the liver, spleen, lymph nodes, bone marrow, etc. According to other data the infection may spread through the blood immediately. People who recover from yellow fever acquire a stable immunity. Prophylactic vaccination against yellow fever is based on this property.

## TREATMENT

During recent years a number of curative serums have been proposed; these are serums of reconvalescent humans and naturally immunised monkeys, and also "antimalarial" (anti-jaundice) equine serum (25 ml); however, there are no convincing proofs of their efficiency.

Symptomatic treatment resolves into strict bed rest, good care, light diet, and abundant drink.

Wide use is made of cardiacs, glucose and normal saline solution infusions, particularly in cases of uncontrollable vomiting. The vomiting is alleviated by giving the patient chips of ice to swallow, by peroral administration of 10-15 drops of 1 per cent cocaine hydrochloride and a 1 : 1,000 solution of adrenalin. The patient is sponged with diluted alcohol and warm water during the hyperthermic periods. Secondary complications are avoided by the prescription of antibiotics.

## PROPHYLAXIS

Efficient and persistent control of the vectors (mosquitoes) of yellow fever and isolation of patients lead to the complete eradication of the disease in populated areas. This has been proved by the now historical examples of the extermination of yellow fever in Havana, New Orleans, Panama, Guayaquil, São Paulo, Rio de Janeiro.

Many years have already passed since the occurrence of the last of the epidemics that formerly harried these cities, terrifying their inhabitants. These areas are now free of yellow fever.

Such excellent results are due to enaction of the following measures:

1. Complete sanitation of the terrain (liquidation of all small water bodies that might serve as breeding places for the mosquitoes in populated areas);
2. Detection of larvae and their destruction in sites of oviposition;
3. Detection of mosquitoes and their extermination by means of DDT. The mosquitoes do not usually re-appear after extermination. The energetic, persistent drive against mosquitoes carried out in Brazil resulted in not one single case of yellow fever having been registered for over a period of several years. As has been pointed out by M. Theiler (1951), the *Aedes* mosquitoes have been completely eradicated throughout the country;
4. Owing to its epidemic force and severity, yellow fever is classified as a Convention disease, i. e., a particularly dangerous infection. International and state measures of protection are taken against it.

The International Sanitary Convention of 1926 pledges all governments to report to neighbouring states and to the International Bureau all cases of yellow fever as a measure for the sanitary protection of state borders.

Sanitary jurisdiction in the U.S.S.R. has made obligatory the immediate report to the health organs of any epidemic case of yellow fever.

As a safeguard against epidemic transmission of yellow fever to areas where conditions are favourable for its appearance ships, planes and trains are specially treated with DDT or pyrethrum flowers.

During epidemics in yellow fever areas any ailing person who is jaundiced is presumed to have yellow fever and is therefore hospitalised in specially equipped hospitals (antimosquito devices, double-door entrances, etc.). Premises occupied by patients are subjected to special insecticidal treatment (DDT, fumigation). Individual prophylaxis is secured by protecting healthy persons against the bites of the mosquito vectors.

Control of epidemic introduction of yellow fever is particularly important in areas where possible vectors of the disease exist. All persons leaving areas in which yellow fever occurs are inoculated before departure (see lower). Upon arrival in areas frequented by yellow fever vectors persons who have not been inoculated are quarantined in specially screened premises until nine days have passed since they left the site of infection. However, the insecticidal measures so highly effective in populated areas and their vicinities have but little worth in the jungles. Therefore vaccination is an essential factor in the prophylaxis of yellow fever. Two strains of an attenuated virus of yellow fever are currently employed. The first (the French vaccine) was obtained from a patient in Dakar. After a series of passages in white mice (intracerebral inoculation) a strain of the virus was obtained that had lost the property of causing fatal infections in rhesus macaques. The second vaccination strain of the virus is 17-D. Inoculation is performed by placing the vaccine, suspended in a gum arabic solution, over a scarified area of the skin (Pelletier vaccination). The vaccine is produced commercially in the form of dehydrated mice brains inoculated with the neurotropic strain of the virus. Immunisation is rapid; a pronounced general reaction is observed in 15 per cent of inoculated people (elevated temperature, indisposition), but commonly no serious complications occur.

The high efficiency of both vaccines has been confirmed by numerous epidemiological tests: the incidence of yellow fever among inoculated people is a rare exception.

Vaccination is usually repeated every four years.



# PSITTACOSIS

---

Psittacosis, or parrot disease (the first name originated in the Greek for parrot—psittakos), is an acute febrile disease mostly characterised by atypical pneumonia; it is caused by a filtrable virus.

## HISTORICAL DATA

Psittacosis was first described by Jürgensen in 1876. The disease attracted particular interest in the years 1929-30 when outbreaks occurred in several American and European countries. In 1930, A. Rubakin established that South American parrots were the chief source of the infection. Maier and Eddie (1933, 1947, 1951) discovered a local psittacosis virus in California in budgerigars and other birds. In 1930, Levinthal, Coles, and Lillie simultaneously discovered elementary corpuscles in the reticuloendothelial cells, while Bedson and Bland proved (1932) that these corpuscles were the pathogens of psittacosis.

## ETIOLOGY

The etiological agent of psittacosis is a filtrable virus, *Rickettsiaformis psittacosis* (Bedson, 1932; Zhdanov a. Kornblit, 1949). Synonyms: *Miyagawanella psittaci* (Lillie), *Ehrlichia psittaci* (Moshkovsky, 1945). This organism is one of the ornithosis viruses. It forms large oval elementary corpuscles (200-350 millimicrons) located in the cells of the reticuloendothelial system; it produces a toxin.

## EPIDEMIOLOGY

Parrots and related birds are both the reservoir and principal source of the infection; the disease in these birds may be manifested by pronounced and even severe forms, or in a latent form. The virus is shed by the bird with its excreta and nasal discharge. The infection has been found both in

untamed parrots living in natural conditions and in domestic pets. Consequently, psittacosis is a natural endemic disease. Man contracts the infection by handling and caring for parrots. The virus commonly penetrates into the human organism by inhalation through the upper respiratory tract, but it may also enter through the skin if a person is bitten by an infected parrot. Infection has also been transmitted by human patients.

### GEOGRAPHICAL DISTRIBUTION

Epidemics of psittacosis have been noted in South America and Australia where the infection existed in parrots in natural conditions; however, the disease also appeared in a number of other countries, including the U.S.S.R., in places where parrots are kept and bred.

### CLINICAL ASPECTS

The incubation period varies from 7 to 30 days, but it may be lowered to 5 days, according to the data of Y. Y. Sorokina (1956). Onset is sudden, with chills, acute headache, rheumatoid pains all over the body, photophobia, great debility; nosebleed is not unusual. The temperature goes up step-wise, attaining its peak of 40-40.5° by the third or fourth day of the disease. The fever is as a rule of the continuous type; its duration is usually 2-4 weeks, and it terminates by lysis. In mild forms the temperature returns to its normal level in 7-8 days.

Clinical findings following the onset of the disease are dyspnea, cyanotic lips, and a cough, either dry, or with a mucoid expectoration that subsequently turns mucopurulent; the sputum may contain an admixture of blood. Physical examinations usually yield very scanty results. The only findings are a shortened percussion sound over limited areas, weakened respiration and some fine and medium moist rales; in rare cases does the pneumonic process involve an entire lobe of the lung. Occasionally a dry pleurisy develops. In some patients the pneumonia is only established by X-ray examination showing confined infiltrates producing faint irregular, blurred shadows. According to Y. Y. Sorokina (1956) these shadows are present from the 9th to the 19th day of the disease, in very rare instances they are perceptible up to the 40th day. K. Meyer (1955) reports that pathological findings during physical examinations of the patient recede by the third week of the disease, while X-ray examinations show a slow resolution of the pneumonia.

Cardiovascular findings are a relative bradycardia, cyanotic lips, hypotension, in severe cases a frequent, weak pulse; occasionally collapse develops.

Neuropsychic symptoms in moderate and severe forms of the disease are insomnia, depression, occasionally delirium and Kernig's sign. The appetite is poor, the tongue coated with a white film; nausea, constipation, or, rarely, loose stools are observed. The blood shows a moderate leukopenia with a prevalence of band cells; sometimes a slight leukocytosis is observed; the ESR is accelerated. Psittacosis relapses are not uncommon.

## **DIAGNOSIS**

Psittacosis and ornithosis are so closely related that it is almost impossible to make a clinical differentiation between them. Diagnosis is greatly facilitated by epidemiological establishment of the source of the infection: the source of psittacosis are parrots, parrakeets, and budgerigars, of ornithosis — pigeons, chickens, ducks, and other birds.

Immunological methods employed for diagnosis are an intradermal allergic test (I. I. Terskikh, 1955), and complement fixation with the patient's serum.

## **PROGNOSIS**

Data published by foreign authors show prognosis for psittacosis to have been very grave prior to the introduction of aureomycin (biomycin) into therapeutic practice; up to 40 per cent of cases terminated lethally. Death took place on the fourth or fifth day of the disease in comatose conditions, or following symptoms of cardiac failure and pulmonary edema in the second or third week. With the advent of aureomycin the mortality rate went down to 2 per cent. Epidemics of psittacosis with non-fatal termination have been observed.

## **PATHOLOGY**

A most characteristic pathologic finding is interstitial pneumonia. The involved areas, greyish-red or purple, are sharply delineated from the normal tissue. Microscopy of the alveoli shows a very considerable increase of fibrin, lymphocytes, macrophages, and desquamated alveolar epithelium, while the neutrophil count is low.

## **TREATMENT**

Best results are obtained with aureomycin (biomycin), given by mouth for five consecutive days, in daily doses of 0.3 g divided into 3-4 portions. Terramycin is also effective; the dosage is as for biomycin. Penicillin and sulfa drugs are practically ineffective.

## **PROPHYLAXIS**

Psittacosis patients must be hospitalised in isolation wards for infectious diseases. Bed-linen and clothing and all things the patients come into contact with are subjected to moist disinfection. Parrot nurseries must be under constant veterinary surveillance; infected birds are immediately destroyed and thorough disinfection of their premises performed.

# LYMPHOGRANULOMA VENEREUM (VENEREAL LYMPHOGRANULOMA)

---

Synonyms: inguinal lymphogranulomatosis, climatic (or tropical) bubo, Durand-Nicolas-Favre disease, fourth venereal disease, paradenitis, esthiomena, lymphogranuloma inguinale.

Lymphogranuloma venereum is a chronic virus infection characterised by lesions of the anogenital area and systemic disorders.

The disease was recognised as an independent nosological unit in 1913 by Durand, Nicolas and Favre. Hellerström and Wassen (1930) and Levaditi (1932) proved the virus nature of the disease experimentally.

## ETIOLOGY

The causative organism is *Miyagawanella lymphogranulomatis*, syn. *Ehrlichia lymphogranulomatis* Moshkovski. This is a filtrable virus belonging to the *Chlamydozoaceae*. It forms inclusion bodies measuring 200 to 250 millimicrons, located in the cytoplasm of the endothelial cells.

## EPIDEMIOLOGY

Infection is usually acquired by genital contact, though it may likewise be contracted by other routes (ordinary contact with patients in caring for them, or during surgical treatment of the buboes).

## GEOGRAPHICAL DISTRIBUTION

Lymphogranuloma venereum is mostly found in seaports of the tropics and subtropics, although it may be encountered anywhere. In the Soviet Union this disease was registered only during the foreign intervention of 1919, and during the Nazi invasion of World War II.

## CLINICAL ASPECTS

A primary lesion appears in a matter of several days after the penetration of the virus into the body. However, this lesion may often pass unnoticed, and then the disease is only diagnosed several weeks, or even two

months after the infection has taken place. As a rule the primary lesion appears on the glans penis and prepuce in the male and on the labia, vaginal walls, and cervix of the uterus in females; it may occasionally be located on the walls of the urethra and in the anal area. When the infection has been contracted by a non-genital route the primary lesions appear on the hands or other parts of the body.

The earliest sign of venereal lymphogranuloma is the formation of a papule or vesicle which ruptures and discloses a shallow greyish ulcer, the so-called lymphogranulomatous chancre. The ulcer is painless and it heals rapidly, leaving no scar. Seven to 14 days after the appearance of the primary lesion inguinal lymphadenitis develops, predominantly in male patients, although it has been described in females, too. At first one lymph node becomes enlarged; its dimensions may approach that of a hen's egg. Later other lymph nodes become involved, fusing among themselves and the surrounding tissues. The result is the formation in one or both groins of tumour-like conglomerates with lumpy surfaces. In due time soft spots appear in the lymph nodes; they break open, forming fistulas from which a creamy pus flows out. The ileocecal nodes are frequently involved in the process, though they do not usually become suppurative. In women the anorectal lymph nodes are frequently affected.

The lymphadenitis is accompanied by systemic disorders in the form of remittent or, less frequently, continuous fevers, poor appetite, nausea, vomiting, muscular pain, weight loss, nosebleed, bronchitis, enlargement of the liver and spleen, secondary anemia, at times allergic skin eruptions. Some patients develop meningoencephalitis.

Conjunctivitis, keratoconjunctivitis and uveitis are not uncommon; ocular findings associated with venereal lymphogranuloma are evident.

The disease drags on for months and years. Lesions of the pelvic lymph nodes disturb lymph circulation in the pelvis, skin and anogenital area. This causes elephantiasis of the external genitalia, ulceration and fistulisation between the rectum and vagina, vagina and urinary bladder, the formation of abscesses in the area of the rectum and vagina. Chronic inflammatory processes in the anorectal area are the cause of the formation of longitudinal or annular strictures and intestinal obstruction. All these lesions are conducive to the development of secondary infections and emaciation, factors that may cause the patient's death.

Besides pronounced and severe forms of the disease mild forms are also observed; the latter are accompanied by a slight fever, indisposition, muscular pain.

### DIAGNOSIS

Diagnosis is established by clinical findings and immunological tests, the most specific of which is the Frei test (intradermal injection of 0.1 ml of pus vaccine). The pus vaccine is prepared with pus obtained from unruptured buboes that is diluted in a five-fold volume of sterile physiological salt solution and heated to 60°C for one hour on three successive days. The reaction is positive if in 48 to 96 hours after the injection of the vaccine a

central hard mass in the papule at the site of vaccination measures  $6 \times 6$  mm or more. Positive results are usually obtainable in 7 to 40 days following the appearance of the lymphadenitis. Aids in diagnosing lymphogranuloma venereum are likewise the complement-fixation reaction and virusoscopy. For the latter investigation a smear of bubo pus is stained by the Romanovsky or Morozov techniques, after which the elementary inclusions may be found under the microscope.

Fatal terminations are rare; however, in absence of proper treatment the disease becomes chronic and it may then lead to severe secondary complications and disablement.

### **PATHOLOGY**

Pathological findings are plasmacytic and histiocytic infiltrates in the sites of lesion, necrosis and suppuration in the lymph nodes and conglomerations of uninucleate cells, chiefly plasmacytes; the neutrophil and eosinophil counts in these areas are low, tubercular nodules are present, in later stages of the disease—fibrosis.

### **TREATMENT**

Therapy is effected with antibiotics and sulfonamides. The antibiotics of choice are biomycin (aureomycin), synthomycin (racemic form of chloramphenicol), and terramycin. Byomycin and synthomycin are administered for 7 to 13 days in daily doses of 3 g and 3-4 g respectively. Terramycin is given in daily doses of 4 g on 14 consecutive days. The sulfa drugs are administered in 5- to 7-day cycles with two-week intervals between cycles: sulfathiazine (Russian sulfadimezin), sulfadiazine (Russ. sulfazin), and sulfathiazole (Russ. norsulfazol) are prescribed in daily doses of 6 g, while sulfapyridine (Russ. sulfidin) is given in daily doses of 4 g (cited from A. M. Krichevsky and V. M. Zhdanov, 1955). Foreign authors report good results with sulfathiazole and sulfadiazine, 6 g on the first day of treatment followed by 3 g daily for 20 days (a total of 66 g) (cited from Manson-Bahr, 1954).

Strictures of the rectum call for surgical intervention.

### **PROPHYLAXIS**

The spread of the disease is prevented by registration and treatment of patients at special out-patient hospitals (dispensaries), by tracing any appearance of the infection to its source, and by sanitary propaganda. A state-organised drive against venereal diseases in the Soviet Union has resulted in the eradication of venereal lymphogranuloma in the country.

# GRANULOMA INGUINALE

---

Synonyms: granuloma venereum, genitoulcerative granuloma, genitoinguinale granuloma, tropical inguinale granuloma, donovanosis, granuloma contagiosa, granuloma pudenda tropicum, ulcerating granuloma of the pudenda.

Granuloma inguinale was first described in India by McLeod in 1882. The causative organism was discovered by Donovan in 1905.

## ETIOLOGY

The disease is caused by a bacillus, *Donovania granulomatis* (Anderson et al., 1943), located in tissue macrophages. The mature parasites are encapsulated, the young forms are not. The capsulate forms, called Donovan bodies, are oval- or bean-shaped, 1-1.5 by 0.5-0.7 microns. With the Romanovsky stain the body of the bacillus is seen to be light-blue and to contain dark-blue or black chromatoid inclusions surrounded by a dense pink substance. The young *Donovania* may appear in the form of cocci, diplococci, and bacilli measuring 0.6 to 1 micron; these forms lie in a non-pigmented zone. Both the capsulate and non-capsulate microorganisms may be observed as dense groups, or cysts, in the macrophages: sometimes one cyst contains both forms.

## EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

Infection is mostly contracted by the genital route, though it may occur otherwise.

Granuloma inguinale is common to Southern China, Indonesia, Thailand, Malaya, India, North Australia, New Guinea, West and Central Africa, Central and South America, the southern states of the U.S.A. (principally the coast of the Gulf of Mexico and the valley of the Mississippi), and the Antilles.

## CLINICAL ASPECTS

The incubation period varies from several days to 4-5 months.

The ulcerations mostly involve the external genitalia, the inguinal, perineal, and perianal areas. Lesions are less frequent on the lips, cheeks, in the nose, pharynx and larynx, on the chest, and in the bones. In 1925, Tierfelder described a liver abscess in the pus of which he had discovered Donovan bodies.

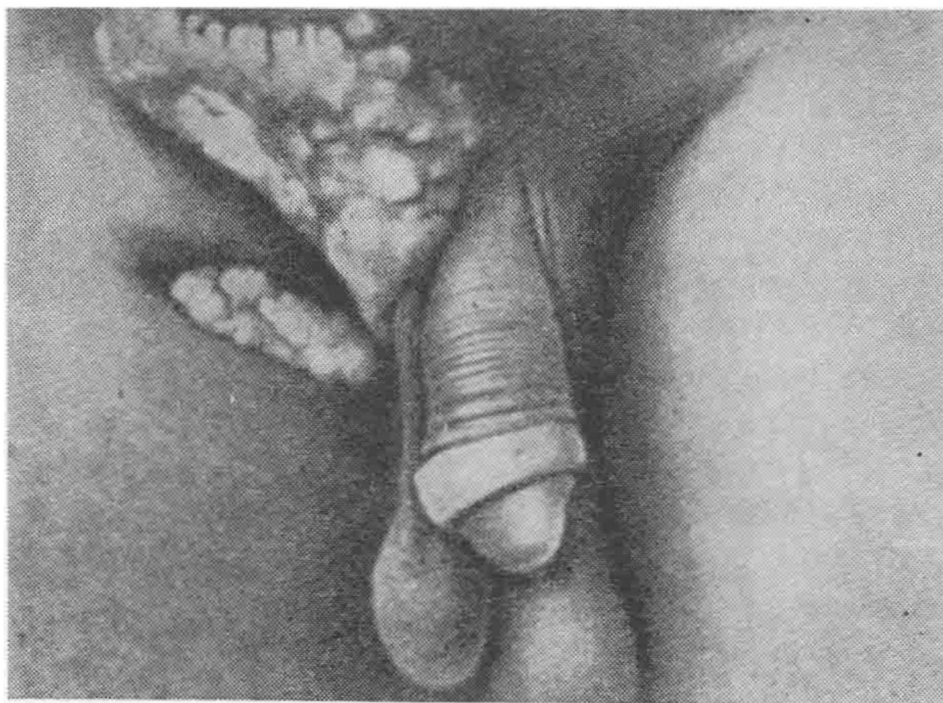


Fig. 123. Granuloma inguinale. Hypertrophic form (Rajam a. Rangian)

The primary lesions may appear as ulcers, papules, or subcutaneous nodes. The most frequent early symptoms are painless, soft, velvety, bright-pink ulcers with wavy serpiginous edges; the ulcers are covered with a serosanguineous exudative film, or with a delicate, transparent, parchment-like crust.

The firm, flat-topped papules measure 25 to 40 mm in diameter; after several days their epithelial covering sloughs off and an ulcer is formed.

Subcutaneous nodes are rare. Such nodes are at first hard, later they soften; after they have broken down or been lanced an ulcer appears in their site.

In males the primary lesions are mostly located on the prepuce and glans penis, in females on the labia minora, pubes, and crura of the clitoris.

The ulcerative process is spread to other parts of the body per continuitatem, for the most part through the clothing and hands of the patient; occasionally it spreads through the blood stream.

There are four forms of the late period of the disease: hypertrophic verrucose, sclerous, exanthematous, and necrotic.

In the hypertrophic form (Fig. 123) a considerable part of the genitalia and adjacent tissues are usually involved. The ulcers are almost painless,



with abundant pale-pink verrucose granulations; a scanty or no exudate is present. The disease develops slowly, over a period of months.

The sclerous form is more common to females; it is characterised by the formation of extensive scars, often resulting in pudendal deformation.

The exanthematous form is characterised by the appearance of solitary or multiple ulcers on the genitalia and in the groins; velvety, bright-red, prolific, moist, bulging granulations hang over the edges of the ulcers. The ulcers discharge an abundant, offensive exudate. Patients complain of intense pain in the ulcers and intolerable pruritus in the genital area.

The necrotic form is the result of a concomitant secondary infection, principally fusospirochetal. The pink granulations develop into a dirty-brown necrotic tissue discharging an abundant chocolate-coloured exudate. The necrotic process spreads both superficially and in depth. In females the vulva, perineum, and perianal area may suffer complete destruction, and a pus-filled cavity may be formed between the rectum and vagina. In males complete or partial destruction of the penis is not infrequent. Symptoms of toxicosis and fever appear, secondary anemia develops. Termination may be lethal.

Granuloma inguinale is usually a chronic disease. Its duration varies from 15 days to 35 years, but  $2\frac{1}{2}$  years is the most usual period. Complications are pseudoelephantiasis of the external sex organs, resulting from compression of the lymphatics, scar stenosis of the urethra, anus, vagina, and mouth, destruction of the penis.

### DIAGNOSIS

Diagnosis is based on clinical data and demonstration of the causative organism. The latter is done in a Romanovsky-stained smear of a particle of tissue removed from the surface of an ulcer with a forceps. A possibility that must be borne in mind is that granuloma inguinale may be accompanied by syphilis, chancroid (soft chancre), or lymphogranuloma venereum; hence a thorough examination of the patient is necessary.

### PROGNOSIS

Inguinal granuloma is seldom the direct cause of death, but at times it leads to a progressive secondary anemia and creates conditions favourable for the onset of a septic infection, pneumonia, pulmonary and intestinal tuberculosis. The disease is probably conducive to the development of cancer of the genitalia, although its importance in this respect is not great.

### TREATMENT

The formerly prescribed antimony preparations have of late been replaced by antibiotics – streptomycin, aureomycin, chloramphenicol. Streptomycin is given intramuscularly for no less than 10 days, in daily doses of 1-2 g, the total dosage for a cycle being 10-20 g.

Occasionally a primary resistance of the *Donovania* to streptomycin is observed.

Aureomycin and chloramphenicol are prescribed perorally, 0.5 g every six hours; the optimal total dosage for a cycle is 20 g.

In the majority of cases directly effective results are obtained with antibiotics: the Donovan bodies disappear in 3 to 15 days, the ulcers heal in 14 to 40 days; however, in some patients relapses are observed over periods varying from several months to two years.

### **PROPHYLAXIS**

The spread of granuloma inguinale should be curbed by a systematic elicitation of patients and their compulsory treatment, by sanitary propaganda, and by setting up a network of specialised out-patient clinics.

# BARTONELLOSIS

---

Synonyms: Oroya fever, verruca peruviana (Peruvian wart) or verruga peruana, Carrion's disease.

Bartonellosis is an infectious disease, characterised in its early stages by fever and hemolytic anemia, and in its late stages by skin lesions.

## HISTORICAL DATA

The disease now called bartonellosis was known as early as the 16th century, when the Spanish forces besieging Peru were severely affected by it. Two distinct diseases were recognised for a long time—Oroya fever and verruga peruana. In 1885, a medical student, Carrion, injected himself with the blood of a verruga peruana patient; the disease Carrion developed manifested the clinical symptoms of Oroya fever, to which he succumbed. By this truly heroic experiment the identity of Oroya fever and verruga peruana was proved. An analogous conclusion was reached by Noguchi (1926, 1927) after he had experimented on monkeys. Andriosola (1898) described some peculiar inclusions in erythrocytes. Barton (1905, 1909) held that these inclusions were protozoans. Strong and his co-workers (1915) named this microorganism, the pathogen of the disease, *Bartonella bacilliformis*.

## ETIOLOGY

The causative agent of bartonellosis is a microorganism closely related to the bacteria—*Bartonella bacilliformis* (Strong et al., 1915). The bartonellas are straight or curved rods, 1.5-2.5 by 0.2-0.5 microns. They possess motility; one end carries a bundle of flagella. V- and Y-shaped and rounded forms are encountered. They parasitise erythrocytes and endothelial cells, predominantly in the lymph nodes, liver, spleen, and intestines. With the Romanovsky technique they stain purplish-red.

## EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

The epidemiological aspect of the disease is not known well enough. The infection is contracted through the bites of sandflies, chiefly *Phlebotomus verrucarum*.

The disease is endemic in Peru, Ecuador, Bolivia, Chile.

## CLINICAL ASPECTS

The incubation period lasts for approximately 3 weeks, sometimes longer. Onset may be gradual or sudden—with fever and chills, headache, pain in the joints, bones, and muscles. The fever may be irregular and undulating. Anemia develops rapidly. In severe forms of the disease the erythrocyte count falls to 1,000,000 or even 500,000 per cu mm of blood, and the colour index is usually low. Erythroblasts appear in the peripheral blood together with a considerable number of normoblasts, polychromatophilic and basophil-stippled erythrocytes; a characteristic feature is macrocytosis; the reticulocyte count increases, sometimes by 50 per cent. Up to 20-30 per cent of the red blood cells are invaded by *Bartonella bacilliformis*. The bilirubin content in blood serum is shown to be increased by the indirect reaction. Consequently, bartonellosis is accompanied by the development of macrocytic hemolytic anemia with a normoblastic type of blood-formation (Ricketts, 1949). White blood counts show a moderate leukocytosis with an increase in the neutrophil count. The liver is frequently enlarged, splenomegaly is rare.

In cases of severe anemia death frequently occurs in the second or third week of the disease; the principal cause of the lethal termination is not uncommonly a secondary salmonella infection. In favourable courses the bartonellas disappear from the erythrocytes quite suddenly, within a period of several days, hemolysis stops, the temperature returns to its normal level, the composition of the blood gradually returns to normal, and the infection gradually passes into a latent phase lasting for about two months. After this period the disease reaches its second stage, characterised by lesions of the skin and, frequently, of the mucous membranes. This stage is called Peruvian wart—verruca peruana. In some patients it develops without the preceding acute stage.

Small or large nodules appear on the skin; there are much more of the first (up to 1,500 in one patient) than of the second. The formation of the small nodules is preceded by the appearance of red spots that gradually become darker and turn into small nodules or papules ranging in size from a pin-head to a pea. These papules are more frequently located on the face and extremities, less frequently on the body. It is not uncommon for them to involve the mucous membranes of the mouth, esophagus, stomach, intestines, vagina, uterus; as a result hemorrhages, sometimes very severe ones, appear in these organs. The papules have been discovered in the lungs, heart, liver, spleen, brain, and membranes of the latter. Frequently small superficial ulcers are formed in the site of the papules. Healing

occurs within several weeks, with no scars remaining. However, relapses with fever and new eruptions are frequent.

The large nodules are not numerous; their location is chiefly the vicinities of the elbow and knee joints. They have the appearance of warty vascular formations ranging in size from a walnut to a pear. They bleed readily, ulcerate and become infected. Healing, after which a scar remains, takes 3-4 months.

### DIAGNOSIS

An acute febrile condition and the development of hemolytic anemia are characteristic of the first stage of the disease. In the second stage the principal manifestation are the Peruvian warts, formations resembling skin lesions in frambesia (yaws). However, in bartonellosis the Wassermann reaction is negative and no treponemas are demonstrable.

During the acute period of the disease blood smear preparations stained with the Romanovsky stain are examined for the presence of *Bartonella bacilliformis*, or a drop of the patient's blood is cultivated on Noguchi serum agar.

### PROGNOSIS

For the acute stage accompanied by severe anemia prognosis is extremely grave—lethal terminations are observed in 10 to 40 per cent of cases. *Verruca peruviana* is not fatal.

### PATHOLOGY AND PATHOGENESIS

Histological investigations performed in the first stage of the disease, formerly called Oroya fever, show central necroses around the hepatic veins, with macrophages and polymorphonuclear infiltration of the necrotic zones; necrotic sites are discovered in the pulp of the spleen; endothelial proliferation and dark-green pigment deposits are seen in the lymph nodes; necrosis, proliferation, macrophagocytosis develop in the bone marrow. The principal factor of pathogenesis is systemic intoxication and hemolysis.

Characteristic features of *verruca peruviana* are endothelial proliferation of the blood vessels and lymphatics, vascularisation, formation of angioendotheliomas with secondary connective tissue growths.

### TREATMENT

Bartonellosis is treated with penicillin, streptomycin, chloromycetin (levorotatory chloramphenicol or levomycetin). These preparations can hardly be considered as having any specific effect on the bartonellas, but they gain control of the secondary infection, first of all of salmonellas, thus preventing the development of complications. Upon the disappearance in the acute stage of the disease of the bartonellas from the erythrocytes

(proof of discontinuance of hemolysis ) blood transfusions are performed; this measure is conducive to a more rapid recovery and it lends the patient a higher resistance to a secondary infection.

### **PROPHYLAXIS**

Prophylactic measures against bartonellosis are extermination of sand-flies and protection against their bites.

# MYCOSES (MYCOTIC DISEASES)

---

## MADUROMYCOSIS

Synonyms: mycetoma, madura foot.

Maduromycosis is a chronic infection affecting the soft tissues and bones of the foot, but it may be found in other parts of the body. The disease has been known since ancient times. The first European to describe it was Kämpfer (1712), while Gill of Madura (India) recognised it as an independent nosological unit in 1842. The fungous nature of the disease was established by H. Vandyke Carter in 1893.

### Etiology

The etiology of maduromycosis is not sufficiently clear. The causative agents are fungi, among which over 50 genera are listed (*Actinomyces*, *Madurella*, etc.).

### Epidemiology

No sufficient study of the epidemiology of this disease has been made yet. Infection probably occurs by penetration of the fungi through skin lesions that are the result of going barefoot.

### Geographical distribution

Maduromycosis is more common to the tropics and subtropics, but cases among local inhabitants of temperate zones have also been described.

Sporadic cases of maduromycosis have been registered in the U.S.S.R. (S. A. Reinberg and S. A. Sviridov, 1956, and other authors).

### Clinical aspects

Weeks, months, and even years may elapse from the penetration of the infection to the appearance of the first symptoms of the disease. First one or several rounded, painless, firm nodules the size of a pea appear. The

skin over them turns purplish-red and brown. After a month or more the nodules soften and break down with discharge of an oily seropurulent, purulent, or sanguineous exudate with a fetid odour; the exudate contains small, often quite numerous, granules (fungi druses), varying in colour — white, yellow, red, black, dark-brown.

As time goes on and new areas of tissue are involved, numerous nodules, sinuses, and fistulas appear. The foot becomes enlarged and deformed. X-ray examinations show the presence of destructive sites in the tubular and small bones. The bones waste away internally and externally, their joints disengage (S. A. Reinberg and S. A. Sviridov, 1956). The disease usually affects only one foot. Sometimes the leg, knee, thigh, even the face, forearm, hand and other parts of the body are involved. The lymph nodes become enlarged only upon the appearance of a secondary infection; no systemic fungous infection nor amyloidosis of the viscera develop.

### **Diagnosis**

Mycetoma of the foot should be differentiated from actinomycosis. The former is distinguished by its benign course, absence of lymphadenitis and/or systemic infection, retention of the supporting and motor function of the limb, and specific X-ray findings. Laboratory diagnosis is established by microscopy of the granules, biopsy, and cultivation of the discharge on Sabouraud's medium.

Prognosis for life is favourable, but the disease is a long and progressive one.

### **Pathology**

The fungi that have penetrated into the tissue are surrounded by infiltrates consisting of lymphocytes, polymorphonuclear leukocytes, and granulated, later fibrous, connective tissue. Vascular findings are thrombophlebitis and endophlebitis. The mycelium of the fungi coils up into granules consisting of cellular detritus, chlamydospores and a dense network of interwoven fungous filaments. At first the granules are surrounded by leukocytes, giant and epithelioid cells, later the number of leukocytes increases and purulent sinuses connected with the nodular fistulas are formed. The elastic tissue is destroyed. Russell's bodies (lipoid droplets) are frequently found. Round cystoid destructive sites are formed in the small and long bones of the foot.

### **Treatment**

Maduromycosis therapy has yet to be developed. Penicillin is not effective. Certain authors (V. D. Kaleman, 1952; S. A. Reinberg and S. A. Sviridov, 1956) have reported favourable results with X-ray therapy. Potassium iodide in large doses and gold preparations are administered. Hopeful results have been obtained with diacetyl-2,2-dioxy-5,5-dichlor-



diphenylsulfide (Reifferscheid and Seeliger, 1955) and 4,4-diaminodiphenylsulfone (Neuhauser, 1955). Ziprokovski and associates (1957) obtained good results with large doses of streptomycin.

### **Prophylaxis**

No prophylactic measures have been evolved.  
It is recommended to protect the feet by wearing shoes.

## **SOUTH AMERICAN BLASTOMYCOSIS (BLASTOMYCOSIS AMERICANA)**

Synonyms: paracoccidioidomycosis, paracoccidioidal granuloma, Lutz-Splendore-Almeida disease, tropical blastomycosis.

South American blastomycosis is a chronic granulomatous disease which predominantly affects the mucous membranes of the mouth and upper respiratory passages; dissemination of the fungous infection involves the lymph nodes, skin, bones, and viscera.

### **Etiology**

The causative organisms are several species of yeast-like fungi: *Paracoccidioides brasiliensis* (de Almeida, 1930) (synonym: *Blastomyces brasiliensis*); *P. cerebriforme* (Moore, 1935); *P. tenuis* (Moore, 1938).

### **Epidemiology**

The pathogenic organism penetrates into the human body through the mucous membranes of the mouth, fauces, and digestive tract; air-borne infection is also possible.

### **Geographical distribution**

South American blastomycosis is endemic to certain parts of Brazil, Bolivia, Peru, Venezuela.

### **Clinical aspects**

The usual initial symptoms of blastomycosis are rapidly ulcerating papules and firm infiltrates appearing on the mucosa of the mouth and fauces; in some cases perforation of the hard palate has been noted. The pathologic process spreads to the tongue, gums, upper respiratory passages, lips, face. Lymphadenitis develops. The process becomes generalised and the papuloulcerative lesions appear on the skin of the trunk and other parts of the body, specific changes occur in the bones and viscera—the lungs, intestines, liver, spleen, and in the central nervous system. A fever develops, accompanied by pains in the chest and a productive

cough; the sputum often contains blood. Pulmonary blastomycosis may be localised, disseminated, infiltrative, cavernous, fibrous; the pleural membranes frequently thicken. The process in the lungs occasionally appears as an initial lesion, without any preceding mucosal lesions in the oral cavity. Digestive system findings: enteritis, in some cases with ulceration of the gastric wall and its perforation.

Del Negro (1954) and his associates have described a fatal case of basal granulomatous meningitis in which the right frontal lobe of the brain was involved.

Blood findings in generalised infections include leukocytosis and secondary anemia.

### **Diagnosis**

The disease is diagnosed by the presence of the characteristic lesions in the mucous membranes of the oral cavity and upper respiratory passages, and also by demonstration of the fungi in scrapings from ulcers and in the sputum. Blastomycosis of the lungs simulates pulmonary tuberculosis; differentiation is attained by examining the sputum for the tubercle bacillus and by special immunological tests.

### **Prognosis**

Blastomycosis americana is a protracted chronic disease which tends to turn into a generalised fungial infection that may result in cachexia and death.

### **Treatment**

Antibiotics and sulfonamides are prescribed.

The antibiotic amphoterrycin B is given intravenously in 5 per cent glucose; 10 ml of the solution should contain no more than 1 mg of the preparation. The initial diurnal dose of amphoterrycin is 0.25 mg per kg of body weight; this dose is increased to 0.5 mg/kg, 1 mg/kg, and if necessary, to 1.5 mg/kg. The solution is given intravenously by drop infusion on alternate days. Duration of treatment is several weeks. Side effects are not uncommon; they include nausea, vomiting, chills, occasionally azotemia. The fever and chills are less marked when 15 mg of prednisone are given by mouth prior to the amphoterrycin infusion and six hours after it.

Another antibiotic is nystatin, given by mouth in sugar-coated pills containing 500,000 units per pill, 6 to 8 times a day. Several 10-14 day courses of treatment are administered.

Sulfadiazine is prescribed per os, 1 g every six hours. This drug is also combined with sulfamerazine: 0.5 g of each drug is given every 3-4 hours. The sulfonamides possess fungistatic properties. Best results are obtained in cases when the blastomycotic lesions involve the skin, mucous membranes and lungs; lymphadenitis shows a greater resistance to treatment. Lesions of the larynx may call for tracheotomy.

No prophylaxis has been evolved to date.

## COCCIDIOIDOMYCOSIS

Synonyms: coccidioidal granuloma, Posadas' disease, San Joaquin Valley fever, desert fever.

Coccidioidomycosis is a chronic disease characterised by allergic and granulomatous skin lesions; generalisation of the infection results in the development of lymphadenitis, osteitis, lesions in the lungs and other visceral organs.

### Etiology

The causative agent is a yeast-like fungus, *Coccidioides immitis* (Rixford a. Gilchrist, 1896).

### Epidemiology

The epidemiological aspect of coccidioidomycosis has been studied very little. The disease has been observed not only in man, but in bovine cattle, sheep, dogs, and rodents, the reservoir and source of the infection. The pathogen probably penetrates into the human system by inhalation and through the skin.

### Geographical distribution

Coccidioidomycosis is common to the south-western states of the U.S.A., has been registered in Central and South America, on the Hawaiian Islands, in Italy, and south-eastern Europe.

### Clinical aspects

The skin lesions due to coccidioidomycosis are of two types – allergic and parasitic (Negroni, 1950-53). The former are characterised by the appearance of a multiple or crust-like nodular cutaneous erythema and urticaria that disappear spontaneously within one to four weeks.

The parasitic lesions may develop in the superficial layers of the skin and in the subcutaneous tissue. These lesions appear in the form of a macular or papular rash, ulcerative fungous granulomas and tumour-like growths resembling cauliflower. Cold abscesses and gummoid granulomas may appear in the subcutaneous tissue.

Involvement of the cervical lymph nodes leads to the development of a pathologic process resembling scrofuloderma; penetration of the fungi into the bones and joints evokes clinical symptoms resembling those observed in maduromycosis. The most frequently affected visceral organs are the lungs. The patient develops a cough with hemoptysis, pains in the chest, dispnea, fever, debility and loses weight. Physical and X-ray examinations show the presence in the lungs of a localised, miliary, or infiltrative process; bronchiectasis and caverns are not uncommon. The latter may range from 1 to 14 cm in diameter; their walls are very thin, and no

infiltrates are, as a rule, formed around them. In some cases exudative pleurisy and pneumothorax occur. Myocarditis, meningitis, lesions of the female genitalia have been described. The clinical forms of coccidioidomycosis vary considerably in severity and symptoms from case to case. Both severe fatal forms and subclinical forms are observed.

### Diagnosis

The disease is diagnosed by immunological tests, the demonstration of the fungi in the sputum, and tissue biopsy.

### Treatment

No truly adequate therapy has been evolved as yet. The preparations used are amphoterrycin, nystatin, and potassium iodide. Surgical intervention is indicated for large caverns in the lungs.

No prophylactic measures have been worked out so far.

## HISTOPLASMOSIS

Synonyms: Darling's disease, Darling's histoplasmosis, the Haneman-Schenker disease.

Histoplasmosis is a mycosis caused by an organism parasitising the reticuloendothelial cells. The condition is accompanied by lesions of the skin and oral mucosa, enlargement of the liver and spleen.

The disease was first described by Darling in Panama in 1906.

The causative agents of histoplasmosis are the fungi *Histoplasma capsulatum* (Darling, 1906), and *H. piriformis* (Haneman-Schenker, 1933).

Histoplasmosis is not essentially a human disease; it also affects cats, dogs, mice, skunks, opossums. Man probably contracts the infection by mouth. It is also quite possible that transmission occurs through insect vectors.

Human histoplasmosis has been described in Central and South America, in the U.S.A., on the Philippines, in Indonesia, in South Africa.

Histoplasmosis is a generalised mycosis accompanied by lesions of the skin, mucous membranes, joints, visceral organs. Papules 0.1 to 0.5 cm in diameter appear on the skin; some of them necrotise and become ulcerative; cutaneous nodules and infiltrates are frequent. Papular eruptions also develop on the mucous membranes of the oral cavity and pharynx, on the lips and dorsum of the tongue. The lymph nodes enlarge. Digestive system findings are esophagitis, proctitis, hepatomegaly. Localised lesions with enlargement of the mediastinal lymph nodes develop in the lungs.

Various forms of histoplasmosis have been described, among them histoplasmosis of the central nervous system, endocardium, bone marrow, middle ear, joints, adrenals. Leukopenia and progressive anemia are observed in the blood. The disease is accompanied by a remittent fever. At late stages cachexial symptoms develop. The duration of histoplasmosis varies from several weeks to 15 years.

The clinical features of histoplasmosis are somewhat similar to those of visceral leishmaniasis. The decisive factor in differentiating these diseases is recovery of fungi from the sputum and biopsy material, as well as examination of sternal bone marrow specimens for leishmaniasis. The allergic test with intradermal injection of histoplasmin is also resorted to.

In pronounced forms of the disease prognosis is usually grave, although cases of spontaneous recovery have been reported.

Therapy is administered with amphotericin and nystatin. Prophylaxis has not been studied.

# POISONOUS FAUNA OF WARM LANDS

---

Poisonous animals have in their systems, either constantly or transiently, substances which are normal to them but cause various degrees of toxicosis in man (Y. N. Pavlovsky).

The poisons of some venomous animals are produced and secreted by special poison glands connected with wound-inflicting apparatus (e. g., the specific venomous glands of the scorpion and its sting). In other creatures, the bedbug, for instance, the function of the poison glands is enacted by the digestive tract, and the pricking apparatus is located in the mouth organs.

Poisonous fauna may be subdivided into armed animals possessing a wound-inflicting apparatus, and unarmed animals devoid of such devices. The routes by which the poisons are delivered vary: some penetrate through the skin, others through the digestive system (poisoning caused by eating certain fish—e.g., the *Schizothorax*).

## BITE OF THE KARAKURT (BLACK WIDOW SPIDER)

Russia first learned of the karakurt from the Russian explorers Gmelin, Pallas, and others. In 1837, a Kharkov researcher, Prof. Krynitsky, published a comprehensive description of this spider, found by him in the vicinity of Odessa in 1827.

The first data on the karakurt in Turkestan were reported by a prominent naturalist and explorer, A. P. Fedchenko (the 1860's). The clinical features of the toxicosis produced by the bite of this spider were described in detail by I. N. Shatilov in 1886, while in 1897, V. P. Zasimovich first reported a death caused by its bite. According to unverified data (K. N. Rossikov) over a thousand karakurt bites were registered in 1895 in Kirghizia and the Kalmyk steppes, and 396 bites in 1896 in the Syr Darya area. Russian literature covering the years 1883-1953 contains a total of 67 descriptions of human beings bitten by the karakurt spider (data of

Y. A. Blagodarny). Among the first authors to describe the clinical features and treatment of conditions due to karakurt bites were A. F. Korovnikov (1920), A. A. Finkel (1929), G. I. Samokhin (1933), Y. N. Pavlovsky and A. V. Gizhitsky (1955). M. I. Maxianovich studied the immunobiological properties of the karakurt venom.

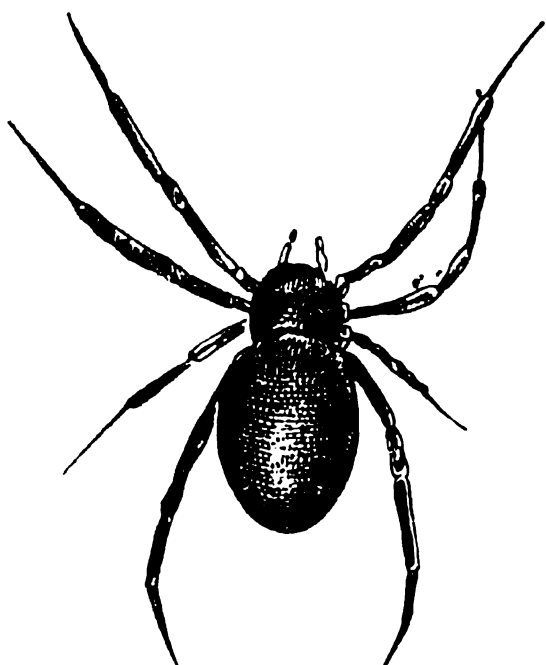


Fig. 124. Black spider *Latrodectus tredecimguttatus* (karakurt)

The most comprehensive studies of the life-history of the karakurt and of the toxic properties of its venom were carried out by P. I. Marikovsky (1947-1953), while the clinical features produced by its bite were described by Y. A. Blagodarny who published a monograph entitled *Bites of the Karakurt* (1956).

### Geographical distribution

The karakurt (black wolf) or black widow spider *Latrodectus 13-guttatus* (also known as *L. lugubris*) is known in Europe as the “malmignatte”; it is closely related to the American black widow spider *Latrodectus mactans*. Its habitat is principally in tropical and subtropical zones. It is quite widespread in the U.S.S.R., as it inhabits the Republics of Central Asia and the Caucasus, the Crimea and Southern Ukraine, the southern reaches of the Volga; in other lands this spider is common to South and East China, the countries of the Middle East, Iran, Afghanistan.

### Morphology and biology

The length of the female karakurt (*Latrodectus tredecimguttatus*) is 1 to 2 cm, while the male is only 8-9 mm long. The velvety-black females occasionally have a bright-red spot on the abdomen. The male is marked (on the ventral surface) with vivid white spots with reddish dots in the centres. The karakurt lives in arid desert zones, making its nests in cracks

of adobe fences and walls, in the burrows of rodents, at the bases of mulberry-trees, in bleached-out skulls, on slopes of gulleys overhung by the sod of wormwood, tamarisk, and other plants.

The karakurt feeds on ants, locusts, grasshoppers, ground beetles, bugs, etc.

At the end of the summer the female oviposits, weaving straw-yellow cocoons for her eggs (she makes as many as 12 cocoons, each one housing from 100 to 600 eggs). The eggs winter in their cocoons, and the young spiders hatch in April of the following year. By June, after a consecutive series of moulting, the spider attains maturity. The fertilised female migrates (May-September). The maximum number of assaults on man are observed during this period, both by day and during the night. By the end of the period of fertilisation the male spider no longer exists, as it either perishes or is devoured by the females (hence the popular name for the spider — “black widow”).

### **Clinical aspects**

In almost half of the people bitten by the karakurt an extremely pronounced reaction is observed at the site of inoculation — a red spot, fluid-filled vesicles, and swelling (Y. A. Blagodarny); at times the local symptoms are insignificant. Patients complain of severe pain and burning sensations.

One of the initial symptoms of the systemic effect of the bite is acute adynamia (Y. A. Blagodarny gives it as appearing in 42.2 per cent of cases). Simultaneously, intensive pain appears in the extremities and lumbar region, and severe headache. In 30 to 50 per cent of cases pain and a sensation of compression in the chest have been noted.

Not all patients have a fever, and if the temperature does rise it is usually only for a short while, or it is of a subfebrile type. However, chilly sensations are frequently experienced.

Cutaneous and mucosal findings include extremely polymorphous symptoms: roseolous, vesicular, papulopustular rashes located variously (chest, abdomen, neck, etc.); these rashes frequently itch intensely. In rare instances edema of the eyelids and face as well as conjunctival hyperemia have been observed.

Data concerning the pulse and arterial pressure is conflicting: in the majority of cases increased arterial pressure and pulse rates have been reported; however, in approximately one third of cases lowered arterial pressure and bradycardia were seen (Y. A. Blagodarny). According to Z. S. Barkagan the karakurt toxin affects the vasculoregulating system, bringing on constriction of the arteries.

The patient's respiration is accelerated; occasionally complaints of not getting enough air and of compression in the chest are made.

Gastrointestinal findings: in 25 per cent of cases — nausea and vomiting, in rare cases — salivation, quite frequently — deglutitory trouble, constipation or diarrhea. A most characteristic symptom in severe cases is the



appearance of acute abdominal pain accompanied by rigidity of the abdominal muscles. Moderate albuminuria and hematuria are noted.

Nervous system findings: frequently psychomotor excitation, occasionally delirium, in rare instances meningeal symptoms, contractions of the extremities, paralysis of the facial nerve, widening of the pupils. Lacrimation and impaired hearing are not uncommon.

Blood findings: moderate leukocytosis with increased neutrophil count, accelerated ESR.

*Mild, medium, and severe forms* (31.5 per cent according to Y. A. Blagodarny) of poisoning are observed. Severe cases sometimes terminate lethally (total rate of fatal terminations up to 4 per cent).

### **Pathology**

Pathology has been studied chiefly in guinea pigs; the findings were edema of the lungs, necrotic lesions in the liver, spleen and adrenals, hyperemia of the brain.

### **Pathogenesis**

The karakurt poison is evidently a toxalbumin. Even a temperature of 60 °C causes its rapid destruction.

The principal effect of the poison on the nervous system is lesion of the central and peripheral sections of the autonomic nervous system (experiments with animals exposed to karakurt bites, observation of human patients [Y. M. Kompaneyetz, 1947]). The clinical features of karakurt poisoning contain considerable elements of anaphylactic shock and capillary involvement, as was quite correctly pointed out by I. I. Moshkovsky and A. M. Okhotina (1945).

### **Treatment**

Therapeutic measures must be taken most urgently as the poison is rapidly absorbed (this was established experimentally).

There have been reports on the complete neutralisation of the karakurt venom by a short application of a burning match to the bite, or a thermocautery, or a red-hot metal rod.

Numerous methods have been proposed for treating the toxic effects of the karakurt bite. The most expedient are set forth.

The injections of potassium permanganate formerly recommended have now been abandoned (as they are always made when it is already too late for them to be of any help); a 1-2 per cent solution of novocain is injected to alleviate pain. A good effect is obtained with the intravenous infusion of 10 ml of 10 per cent magnesium sulfate, or 10 ml of 10 per cent calcium gluconate, and also with intramuscular injections of magnesium sulfate.

It is recommended to treat grave systemic symptoms by instituting a paranephritic block with 0.25 per cent novocain, by the intravenous injection of 5-10 ml of 1 per cent novocain (T. A. Arustanyan), by the injection of 1 per cent morphine and 1 per cent promedol (1 ml) (promedol is 1,2,5-trimethyl-4-phenyl-4-propionhydroxypiperidine hydrochlorate). For severe cardiovascular conditions injections of cordiamin (25 per cent solution of diethylnicotinamide), camphor or strophanthin are recommended (0.5 ml of an 0.05 per cent solution intravenously or intramuscularly).

### Prophylaxis

The only protection against karakurt bites is wearing shoes during field work, not lying down on the bare ground, covering oneself with gauze bed-nets when sleeping outdoors, and keeping one's clothing inside the net.

### SCORPIONS (SCORPIONIDA)

Scorpions (genus *Buthus* and others) are arachnids of the order *Scorpionida*. They are inhabitants of many southern countries; in the U.S.S.R. they live in the arid semi-deserts of Central Asia, on the Caucasian coast

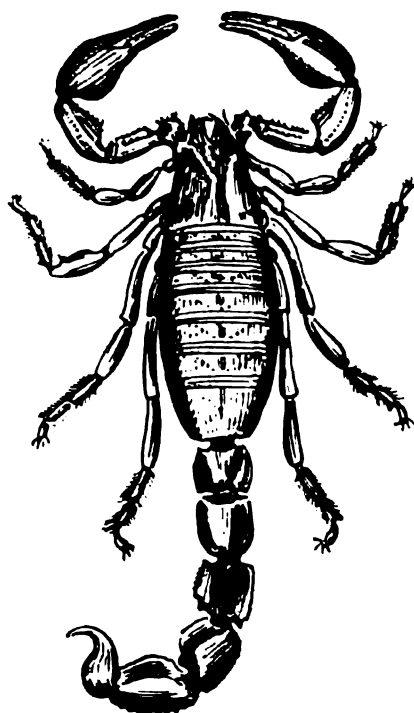


Fig. 125. Scorpion

of the Black Sea, in Armenia. Tropical scorpions (African, Mexican, Brazilian, etc.) are particularly venomous. During the daytime these arthropods hide under stones, in burrows, in cracks of adobe fences and walls, in tents, etc. At night they creep into beds, socks, shoes, clothes.

The length of a typical scorpion varies from 2-3 to 5-6 cm, its breadth is up to 1 cm over the abdomen and 2-3 mm at the tail end. The skin of the tail end is furnished with a poison vesicle pulled out into a sharp, curved sting several millimetres long, with two poison glands. In order to sting

its victim the scorpion curves its tail forward over its body and strikes. As soon as the sting pricks the skin the poison is ejected from the glands as a reflex action (Fig. 125).

### **Symptoms of poisoning**

Severe, often intolerable, protracted pain in the point of injection; the site immediately swells, and the swelling rapidly spreads over a large area. At times blebs are formed at the site of the sting. Fatal cases among young children have been described. Considerable debility is frequently observed as well as general collapse, weak pulse, tachycardia, headache, vomiting, diarrhea, early and late paroxysms of suffocation, profuse perspiration, and abundant salivation.

### **Treatment**

Hospitalisation is not obligatory. A series of injections with 2 per cent novocain should be done as soon as possible around the site of the sting. It has been reported by Z. S. Barkagan that the toxic symptoms are rapidly alleviated by injections of atropine. Manifestations of systemic toxicosis are treated with intravenous infusions of glucose or calcium chloride; cardiacs (camphor, cardiazol, caffeine) are injected upon the appearance of severe generalised symptoms and collapse. Warmth is essential, also fluid intake in abundance.

## **POISONOUS BEETLES**

Among the unarmed poisonous beetles harmful to man are *Paederus albipilis*, *P. fuscipes* and the blister beetles *Mylabris frolovi*, *M. triangulifera*, *M. calida*, and *M. elegantissima*. The various species of *Paederus* congregate near water and man is poisoned by crushing their bodies.

### **Symptoms of poisoning**

Y. N. Pavlovsky and A. K. Stein studied the toxicity of beetles of the genus *Mylabris* and found it to be similar to that of blister beetles of the Spanish fly type (*Lytta vesicatoria*).

An oily emulsion prepared with crushed blister beetles causes vesicular dermatitis upon application to the skin (the process occurs in the epidermis).

The lymph of these beetles, coming into contact with human skin, causes an intense burning and itching; papules and vesicles soon form, and some swelling of the skin takes place (both the epidermis and dermal connective tissue are involved). Contamination of the conjunctiva with the venomous fluid is particularly dangerous as it results in severe conjunctivitis and keratitis. Another danger is secondary coccoid infection of the skin and conjunctiva.

## Treatment

Therapy consists of powdering the affected areas of skin and applying sedative preparations; conjunctivitis is treated by the instillation of albucid drops, protargol, etc.

## SNAKE BITE POISONING

The symptoms and severity of toxicosis caused by the bite of venomous snakes vary depending on the species of snake, site and depth of bite, volume of venom injected, and the reactivity of the victim's system. The venom of vipers is hematoxic; poisoning is characterised clinically by the fulminating onset of local symptoms — persistent pain, considerable edema, hemorrhages, necrosis; cobra venom is predominantly neurotoxic, causing paralysis.

### Principal species of venomous snakes

Over 200 species of such snakes are known, the majority of which live in tropical and subtropical countries. The species that are most frequently responsible for snake bite belong to the *Viperidae* and *Elapidae* families; certain marine snakes are also highly poisonous. The family of vipers (*Viperidae*) falls into two sub-divisions — true vipers (*Viperinae*) and pit vipers (*Crotalinae*). Some true vipers are the adder or common viper *Vipera berus*, the steppe viper *Vipera renardi (ursini)*, the sand viper *V. ammodytes*, the Armenian viper *V. raddei*, *V. lebetina*, the saw-scaled viper *Echis carinatus*, the Persian viper *Pseudocerastes persicus*, the African viper *Bitis arietans*, etc. Poisonous pit vipers include the copperhead *Ancistrodon (Angkistrodon) halys*, the diamondback rattlesnake *Crotalus adamenteus*, and others. The asp family (*Elapidae*) is represented by the cobra (*Naja naja*) and the coral snake (*Elaps corallinus*). The most poisonous of the sea snakes (*Hydrophiinae*) are *Pelamidrus platurus* and *Distira cyanocincta*.

### Clinical aspects of snake bite

Bites inflicted by true vipers and *Ancistrodon* pit vipers are immediately followed by acute pain and rapid edema involving the bitten extremity and adjacent parts of the body. Petechial and hemorrhagic spots appear on the skin near the site of the wound and at some distance from it. Hemorrhage also occurs in the mucous membranes of the mouth, and in the visceral organs — the stomach, kidneys, lung, heart. An abscess frequently forms at the site of the wound; an open ulcer remains for a long time after the abscess has broken down. Occasionally necrosis of the tissues follows, revealing the underlying bones. The local symptoms are accompanied by chills and fever, dizziness, syncope, somnolence, or, quite the opposite, excitation, convulsions, vomiting (at times hematemesis),

nosebleed, hematuria. In cases of moderate toxicosis the swelling decreases and the general state gradually improves. The period of convalescence may be protracted to 2-3 and more months. In severe poisoning the patient succumbs to increasing cardiovascular failure within 10 to 14 days after the bite. Cobra bites cause an acute pain that lasts about three hours. The tissues swell up less noticeably than following viper bites. The skin in the edematous site remains normal, or only slightly reddish. A sanguineous fluid oozes from the wound; no ecchymosis is commonly observed. The patient's temperature is normal or subfebrile. Thirty minutes after the bite extreme weakness and pallor develop, followed by nausea, vomiting and laboured respiration. Soon paralysis of the extremities appears, spreading to the muscles of the trunk and head; incontinence of feces and urine develops, disturbance of speech and deglutition becomes evident. In severe cases death occurs within one to 24 hours, sometimes even as soon as 30 minutes following the bite. In milder cases the paralysis disappears, the toxin is eliminated by the kidneys within a day or two, and the patient soon recovers. It is a point worth remembering that the cobra often ejects its venom over a distance of 1.5 metres. Contact with the eyes causes intense pain and conjunctivitis; generally no systemic symptoms appear in such cases, although occasionally the poison may be absorbed and then cause toxicosis with attendant paralysis.

The toxic symptoms caused by bites of poisonous sea snakes are similar to those observed following cobra bites.

### **Diagnosis**

Diagnosis is established by the presence of characteristic symptoms and examination of the fang marks. The fangs of poisonous snakes often leave marks in the form of large spots between which smaller marks made by the non-poisonous teeth are seen.

### **Prognosis**

Prognosis is very grave in cases of severe toxicosis. The mortality rate among people bitten by the most toxic of poisonous snakes (the cobra, etc.) was as high as 30 per cent prior to the introduction of therapeutic serums.

### **Pathology and pathogenesis**

The toxicosis following snake bite causes fatty degeneration of the hepatic cells and the myocardium, exudation into Bowman's capsule of the kidneys, necrosis and sloughing of the epithelium; small sites of infarction are found in the lungs, granular degeneration of the Nissl bodies and fatty degeneration of the anterior branches of the spinal cord are observed. The venoms of the cobra, pit viper, and rattlesnake possess anticoagulative properties; on the other hand, the venom of true vipers

intensifies coagulation. Snake venoms contain hemorrhagin and cytolsin, agents that decompose the vascular endothelium, leading to hemorrhages and hemolysis. Cobra poison contains a neurotoxin that affects the central and peripheral nervous systems.

### **Treatment**

Specific measures for treating snake bite are antislakebite serums prepared by immunising horses against snake venom. These serums are either mono- or polyvalent. However, the antitoxic properties of the first are valid for a group of snake toxins. Thus the antislakebite serum prepared against the bite of the saw-scaled viper *Echis carinatus* is just as effective against the bite of the gyurza *Vipera lebetina*, while the anti-gyurza serum may be given for the *Vipera renardi*, *raddei*, and *berus*. The serum is injected subcutaneously and intramuscularly, in the area of the fang marks, in 10 to 20 ml doses. If the anti-epha (saw-scaled viper) serum is administered for the bite of the gyurza (*V. lebetina*) it is given in an increased dosage (40 ml). When treatment is administered later than 30 minutes after the patient has been bitten he is injected intravenously with 20 ml of the serum. It is recommended to inject 1 ml of the serum 20 minutes prior to injecting the full dose.

Cobra bites are treated by a slow intravenous infusion (conducted for 20 to 30 minutes) of 80-100 ml of serum prepared against the venoms of the gyurza (*Vipera lebetina*), the epha or saw-scaled viper (*Echis carinatus*), or the cobra (*Naja naja*). Upon contamination of the eyes with cobra venom the latter should be washed out with diluted milk, and then several drops of the specific serum instilled into the conjunctival sac. General measures: hemotransfusion counteracts the hemotoxic effect of snake venom. The patient's condition is considerably alleviated by the injection of normal saline solution, cardiacs, and intravenous injections of calcium chloride; cobra venom toxicosis is also treated by artificial respiration and the inhalation of oxygen. Abundant fluid intake (warm) is recommended in order to accelerate renal elimination of the venom.

### **Prophylaxis**

Prevention of snake bite is effected by the extermination of snakes. In India the mongoose is kept as a domestic pet — this animal kills venomous snakes. Other active enemies of snakes are hedgehogs, weasels, polecats (skunks), foxes, pigs, snake-eating eagles, storks, crows, and the secretary-bird. Individual prophylaxis is secured by careful examination of camping places, and by wearing high boots with leather tops. In visiting areas frequented by snakes one should carry a first-aid kit with all that is necessary for treating snake bite.

## SPRUE

---

Sprue is a specific disease of the tropics and subtropics. Its symptoms are persistent fermentative diarrhea, glossitis and anemia, the latter usually of a normochromatic type.

Synonyms: the generally accepted name of "sprue" springs from the Dutch "sprouw", meaning froth; the name was proposed by Patrick Manson in 1879. French tropic-clinicians described the disease under the name of diarrhée de Cochinchine (i.g., Cochin-China or Indo-China diarrhea); it has also been called aphthous cachexia and tropical aphtha, hill diarrhea, white diarrhea (diarrhea alba), tropical diarrhea, psilosis, psilosis linguae, Ceylon sore mouth, tropical sprue.

### HISTORICAL DATA

The first information on sprue under the name of "inlandiche sprouw" is given in a treatise on leprosy in the East Indies in 1687; the treatise points out the presence of lesions of the oral cavity, esophagus, and intestines.

One of the best works on sprue was written by Hillary who described it in great detail on the island of Barbados in 1759.

Sprue has been known for a long time in Central Asia. Among the Uzbeks "chillyashir" (after the Persian word for "forty") was a disease of ill fame, accompanied by frothy diarrhea and inflammation of the tongue; mostly women were affected by it, within 40 days after childbirth, and this gave rise to its name (data communicated by A. A. Askarov and T. H. Nazhmitdinov, Tashkent). Sprue was described in the middle of the 19th century on the peninsula of Indo-China as "Cochin-China dysentery". In 1879, P. Manson wrote a report on the disease and proposed its present name, "sprue". In the Soviet Union the first comprehensive description of sprue and the concomitant anemia was made by A. N. Kryukov in 1922.

## GEOGRAPHICAL DISTRIBUTION

Sprue is a disease common to warm lands with tropical and subtropical climates (Indonesia, India, Ceylon, Burma, Thailand, Cambodia, China, the tropical zone of the American continents, tropical Africa, Australia, etc.), although it is also encountered in warm lands where the climate is more continental—Central Asia, Iran, Afghanistan, Iraq, North Africa, Japan, etc., and also, infrequently, in more northerly lands.

## CLINICAL ASPECTS

Complicated nutritional disorders are prominent in the progress of the disease (malnutrition), and its symptom-complex is predominated by protracted diarrhea. Consequently, clinical findings always show symptoms of systemic nutritional disturbances, so-called alimentary dystrophy, creating a generalised dystrophic background with numerous symptomatic variants (cachexial symptoms, edema, hypovitaminosis B<sub>2</sub>, C, B<sub>12</sub>, symptoms of ulcerative colitis, etc.). However, the leading syndrome of sprue combines the following four features: 1) persistent fermentative enteritis; 2) glossitis; 3) lesion of the hematopoietic system; 4) general emaciation with pronounced neuroendocrine pathology (Fig. 126).

The onset of the disease is insidious. It is most commonly observed in people whose diets are deficient (principally in carbohydrates), in pregnant or nursing women, and in old people. Most prominent are the increasing intestinal symptoms: a markedly swollen abdomen with intensive flatulence, sensation of heaviness and pressure in the middle and lower abdomen. At the same time more or less constant pains are noted in the lower abdomen, and loud borborygmi. The abdomen becomes greatly extended; the patient is so emaciated that the intestinal loops are visible; percussion elicits a loud intestinal tympany; turbulent peristalsis and borborygmus are defined by auscultation. The intensive swelling and rumbling of the intestines is followed by the passage of a voluminous frothy stool, that is frequently almost devoid of pigment (diarrhea alba), after which the patient feels some relief, as the symptoms of systemic toxicosis and severe local symptoms disappear.

The loose stools are passed repeatedly, from 3 to 8 times a day; the stool is mostly loose and voluminous; however, the large intestine is frequently irritated by the acid fermenting mass delivered by the small intestine, and this brings on the development of colitic symptoms (tenesmus, periodic passage of a scanty, mucoid stool). A salient microscopic finding in the fecal matter is the high content of undigested muscular fibres, connective tissue, fat, and fatty acids. Prominent in the intestinal flora are yeast fungi. Decoloration of the feces depends on a peculiar light-coloured variety of urobilin—leukourobilin. Among the clinical features of the intestinal disorder the most vivid is the failure of carbohydrate assimilation. The non-assimilated carbohydrates undergo acid fermentation and methane putrefaction. The gigantic multiplication of yeast fungi



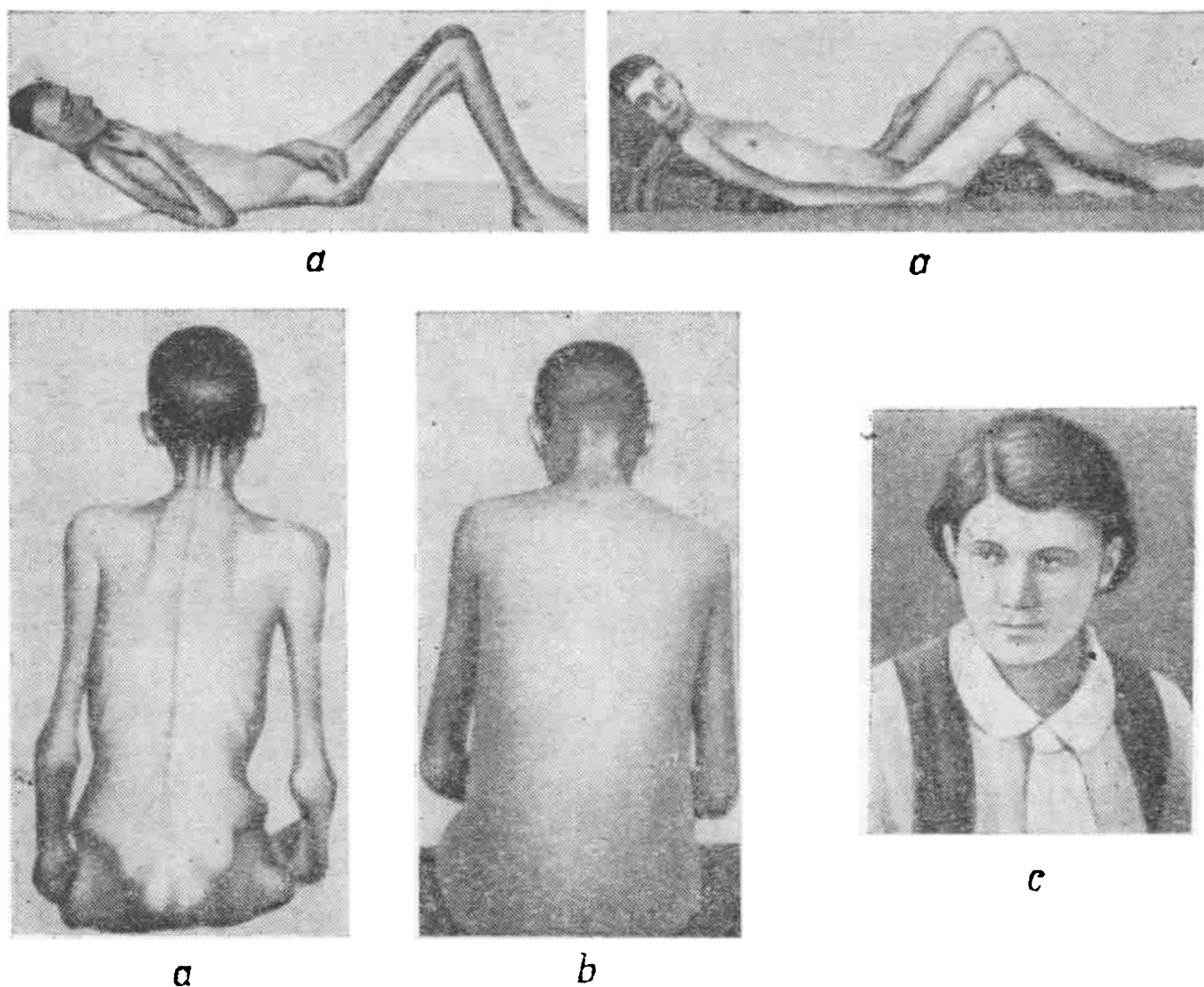


Fig. 126. Sprue  
a — before treatment; b, c — after treatment

(particularly *Monilia psilosis*) in a carbohydrate medium results in acid fermentation. The fermentative contents of the small intestine, with their high level of protein exudates secreted by the inflamed intestine and their acid substances, irritate the intestinal mucosa, while the absorption of these products causes acute toxicosis. It should be borne in mind that besides the fermentative processes occurring in the intestine in fermentative enteritis putrefactive processes with the formation of proteinogenic amines also develop (I. A. Kassirsky, E. I. Atakhanov); the presence of an acid medium activates the process of decarboxylation of carbon dioxide molecules and their conversion into toxic amino products. A number of various species of microbes participate in the formation of putrescent substances—putrescine from ornithine, and arginine and cadaverine from lysine.

The protracted persistent enteritis leads to extreme emaciation and dehydration of the body: a secondary (endogenous) alimentary dystrophy, and also endogenous polyavitaminosis (principally deficiency of vitamins B<sub>1</sub>, B<sub>2</sub>, B<sub>6</sub>, B<sub>12</sub>, C and D) develop.

*Blood findings* are not uniform: the anemia associated with sprue intensifies with the stage of the disease and the increase of vitamin B<sub>12</sub> and

folic acid deficiencies. A normocytic type of extremely pronounced anemia is most characteristic of sprue. The anemia is usually normo- or hyperchromatic.

The anisocytosis observed in this type of anemia is not so markedly macrocytic as in pernicious anemia, while poikilocytosis is entirely absent. The colour index varies, depending on the prevalence of macrocytes or microcytes. Granulocytopenia is not uncommon in the white blood, while in severe cases hyp thrombocytosis and hemorrhagic diathesis are observed.

In some instances, even with young patients, the authors have observed the transition of very protracted sprue that had repeatedly responded to specific anti-enteritic therapy into typical pernicious anemia with megaloblastic bone marrow blood formation. This transition was evidently the result of complete inhibition of folic acid production in the intestines (owing to intestinal dysbacteriosis caused by the prevalence of fungal flora), or of atrophy, following general emaciation and polyavitaminosis of the mucosa of the fornix of the stomach and, consequently, of the auxiliary mucoid cells. If the latter be the case in sprue, for which hypoacid secretion is typical, organic achylia develops.

*Bone marrow hematopoiesis.* Previously A. N. Kryukov and his school, having devoted themselves to a detailed study of blood-formation in sprue, held that megaloblastic hematopoiesis was characteristic of this disease. There were two causes for this conclusion: 1) in accordance with the teachings of Kryukov the macronormoblastic series were counted as megaloblasts; 2) bone marrow blood-formation was mostly studied in cases of considerable anemia and severe forms of sprue, when vitamin B<sub>12</sub> and folic acid deficiencies were naturally to be expected.

In ordinary cases of sprue erythrocytopoiesis proceeds principally through the macrogenerations of the erythroblasts and their derivatives, the macronormoblasts. Typical megaloblasts, demonstrating all developmental phases from the basophilic promegaloblast with its delicate chromatin structure to the orthochromatic megaloblast with its pycnotic nucleus, are also found in the bone marrow; however, megaloblastic transformations in the bone marrow are rarely observed (conversion of sprue into pernicious anemia).

The formation of leukocytes and thrombocytes in the bone marrow is somewhat deficient, as manifested by a certain degree of inhibition of granulocyte maturation and by the polymorphism of the megakaryocyte nuclei. As a whole, the blood-formation abnormalities seen in sprue are caused by a deficiency of hematopoietic factors—folic acid, vitamin B<sub>12</sub> (U. I. Yuldashev)—and other substances necessary for the normal development of erythrocytes, granulocytes, and thrombocytes.

The glossitis attendant on sprue is probably associated with folic and nicotinic acid deficiencies; atrophy of the papillae of the tongue makes the latter look as if it were polished; the sides, and sometimes the dorsum of the tongue too, become inflamed and red, the surface eroded, erosive-inflammatory signs appear on the mucous membrane of the mouth,

palate, pharynx, esophagus. In sprue glossitis is a more pronounced and constant symptom than in pernicious anemia (Fig. 127). An important factor in the development of the symptom-complex of sprue is endocrinopathy. The frequent and predominant development of sprue during pregnancy, following childbirth, and in old age emphasises the pathogenetic ties of the disease with endocrine pathology. Far advanced symptoms of alimentary dystrophy are accompanied by secondary signs of endocrinopathy—atrophy of the thyroid and parathyroid glands with hypothyroidism and hypocalcemia, atrophy of the gonads with the onset of amenorrhea in women and impotence in men, and by the gradual development of symptoms of addisonism—weakness, emaciation, dark pigmentation of the skin. The diencephalic zone is the part of the brain most acutely affected in sprue; this is manifested by symptoms of hypopituitary insufficiency: in extremely advanced cachexia a typical picture of Simmond's disease (hypophyseal cachexia) accompanied by diabetes insipidus and pluriglandular insufficiency is observed. In such cases prognosis, as a rule, is very grave.

Nervous system abnormalities are characterised by trophic disorders associated with lesion of the diencephalon, and with polyneuritis resembling that of beriberi, a result of progressive vitamin B<sub>1</sub> deficiency.

*Classification.* Distinctions must be made between the following: 1) *severe forms* of sprue usually complicated by alimentary dystrophy and polyavitaminosis; 2) *terminal forms* complicated by pluriglandular insufficiency; 3) *moderate forms* complicated by mild symptoms of alimentary insufficiency; 4) *mild forms* bordering on protracted cyclic chronic fermentative enteritis of warm lands.

## ETIOLOGY AND PATHOGENESIS

Sprue is evidently no nosologic entity, but a peculiar syndrome in the origin of which a prominent factor is the unusual development of fermentative processes in the intestines. It is namely in this factor that the elements of the specific etiology of the disease should be sought. This is also the basis of the purely unitary—fungal—theory of sprue. Ashford, for instance, holds that the yeast *Monilia psilosis* is the specific etiologic agent of sprue and that the essential point of the disease is toxicosis caused by this fungus. In substantiation of this assumption Ashford points out the moniliasis that develops in the intestines, esophagus, and oral cavity in sprue patients, stressing the fact that the yeast fungi are recovered from the intestine and mouth in 100 per cent of sprue cases, and only in 15 per cent of healthy subjects. Ashford succeeded in provoking stomatitis and diarrhea in experimental animals by the injection of pathogenic strains of *Monilia psilosis*.

However, the present authors are of the opinion that the pathogenesis of sprue is much more intricate. The combined effect of exogenous factors (dietary deficiency, warm climate) and endogenous factors (e.g., endocrine hypofunction associated with pregnancy or post-middle-age

involution) create conditions contributive to inhibition of the functions of the digestive glands. At the same time a pre-eminently carbohydrate diet overburdens the intestinal tract and promotes the gigantic development of yeast fungi. Consequently, we deal here with no exogenous fungal infection (the exogenous pathogenic fungi include the *Rhinosporidia*, *South American Blastomycetes*, *Actinomyces*), but rather with the development of an endogenous fungal flora of the type of torulosis (cryptococcosis) or moniliasis. There are over 30 species of *Torula* (*Cryptococcus*) and *Monilia* (*Candida*) yeasts with over 87 different names. They live in the oral cavity, the intestines, on the skin, not uncommonly in symbiosis with microbes, they are found on fruit, in milk and milk products. Their characteristic features are, besides the formation of blastophores, the development of a pseudomycelium.

The stupendous multiplication of the fungal flora leads to the development of fermentative and even putrefactive (owing to methane putrefaction of carbohydrates) processes in the intestine that invariably result in persistent diarrhea, emaciation and polyvitamin deficiencies (secondary, endogenous). Subsequently the fermentative process in the intestine becomes the dominant pathogenetic factor of the disease. The clinical features of the hematological syndrome of sprue are influenced by abnormalities in the processes of biosynthesis and assimilation of a number of vitamins, particularly riboflavin (vitamin B<sub>2</sub>), nicotinic acid (P-P factor), and folic (pteroylglutamic) acid (anti-anemia factor or vitamin B<sub>9</sub>). (It is known that in physiological conditions the biosynthesis of vitamins is disturbed by intestinal saprophytes, while in sprue dysbacteriosis develops.) The leading feature in the pathogenesis of pernicious anemia is the absence of a gastric factor—gastromucoprotein, and this leads to the defective assimilation of vitamin B<sub>12</sub>; however, the intestinal factor, i.e., defective formation and assimilation of folic acid in the affected intestine is the most prominent in the anemia concomitant with sprue (clinical data of I. B. Likhtziyer [Dushanbeh] and E. I. Atakhanov [Tashkent]).

Glossitis, an important clinical symptom in sprue, is probably the result of nicotinic and folic acid deficiencies. The emaciation pathogenesis is associated with alimentary dystrophy of an intestinal (endogenous) nature. General emaciation and toxicosis lead to the development of one of the gravest complications of sprue—polyendocrinopathy.

### PROGNOSIS

Prognosis depends on the severity of the disease. In mild and moderate forms expedient therapy leads to complete recovery. Prognosis is poor for severe forms complicated by progressive polyavitaminosis, dystrophy, and terminal hypophyseal cachexia.

### TREATMENT

See following chapter.

## PROTRACTED ENTERITIS OF WARM LANDS

---

The protracted intestinal diseases of warm lands are doubtlessly connected with the effects of heat and nutrition on the human body (the use of coarse kinds of bread and the prevalence in the summer of carbohydrate foods rich in cellulose). Mostly children are affected by these diseases, but they are also frequent among elderly people, taking a leading place in the pathology of hot climates (as evidenced by the predominance of patients with intestinal troubles in the hospitals and out-patient polyclinics of such countries). The unusual variability in the clinical findings of intestinal diseases is astonishing.

The intestinal diseases most widespread in warm climates are acute, subacute, and chronic enteritis and resultant enterocolitis that are often erroneously diagnosed and treated as primary chronic colitis, while in reality they originate in primary fermentative enteritis.

The salient feature of chronic intestinal disorders of warm lands is their association with fermentative processes.

M. I. Slonim, a researcher who studied intestinal pathology in Central Asia for a period of 45 years, pointed out that no less than 50-60 per cent of all intestinal diseases in hot climates were accompanied by symptoms described for sprue, although in milder forms. These troubles are characterised by intensive flatulence, frothy, fluid and voluminous stools, acid reaction of feces, high organic acid values in feces, etc. As a rule, these enteritic disorders appear in the period of summer heat, during the fruit and vegetable season. Excessive ingestion of fruits rich in sugar and cellulose that are, besides, frequently over-ripe and fermenting (melons, grapes), of vegetables, part of which may also be turning sour (tomatoes) accompanied by acute protein and fat deficiencies lead to the onset of fermentative dyspepsia: the intestines of children and of adults alike swell up, their stools become loose, and occasionally severe acute enteritis appears. A considerable part of this type of enteritis terminates in recovery. However, it may become protracted and turn into chronic enterocolitis if the patient's diet is habitually poor, so that he is noticeably emaciated, or if

an intestinal infection (amebiasis, balantidiasis, or bacillary dysentery) that may convert to chronic ulcerative colitis develops (I. B. Likhtziyer, N. S. Polyansky, Dushanbeh, 1955). Moreover, the fermentative processes do not take place in the small intestine alone; they also occur in the cecum, and the acid masses delivered to the ascending, transverse, and descending parts of the colon cause irritation and thereby support the ulcerative-inflammatory process developing in the colon under the influence of infection and alimentary disorders.

Investigations carried out in the clinic headed by E. I. Atakhanov (Tashkent, 1957) have shown that the products formed in the intestines obstruct the normal process of phosphorylation necessary for the assimilation of carbohydrates. Non-assimilation of proteins, fats, carbohydrates and vitamins in the small intestine brings on the development of endogenous alimentary dystrophy and of vitamin deficiencies—polyavitaminosis; clinical findings in the latter may show prevailing symptoms of sprue, pellagra, or B<sub>1</sub>-avitaminosis, or one form of vitamin deficiency may be replaced by another in the progress of the disease.

If such a chronic enterocolitis is accompanied by the development of glossitis and anemia, it converts into true sprue, while the appearance of a typical symmetric dermatitis establishes the prevalence of a pellagra syndrome.

As in the above vitamin deficiencies, patients with chronic fermentative enteritis exhibit symptoms of one or another form of endocrine insufficiency—either adrenal hypofunction with arterial hypotension and diffuse pigmentation of the skin, or a hypophyseal cachexial syndrome (diabetes insipidus), or scurvy, or vitamin B<sub>1</sub>-deficiency, etc. As in sprue, severe lesions of the endocrine system, particularly the cachexial syndrome, are irreversible. Its manifestations are extreme emaciation (“skin and bones”), polyuria, hyposthenuria, rapid elimination of metabolites owing, evidently, to hypofunction of the adrenal cortex. The anterior lobe of the pituitary is most affected, leading to the clinical picture of cerebro-endocrine emaciation (I. A. Rasulev); however, other endocrine glands are also involved in the process, as is revealed by a variegated range of other endocrine disorders—from weakly delineated to definitely pronounced symptoms of hypogenitalism, hypothyroidism, addisonism, etc.

The nervous system is the last to become involved in the pathological process, but its involvement is associated with protracted alimentary insufficiency, when the diencephalic syndrome is particularly marked. Histologic studies of cross-sections show part of the ganglionic cells in the diencephalon to be pycnotic, with shriveled, intensely staining nuclei; clumps of brown pigment are seen in the cytoplasm of the majority of cells; in part of them the Nissl granules disappear, and cytoplasmatic vacuolisation is infrequently observed (T. G. Terekhova).

The course of chronic fermentative enteritis is manifold; it depends on the intensity of the pathologic process and the degree of reversibility of the morphologic changes in the digestive tract and most important organs and systems (mostly the endocrine and nervous systems).



## TREATMENT OF SPRUE AND CHRONIC FERMENTATIVE ENTERITIS

The treatment of sprue and of protracted fermentative enteritis is identical both in principle and in practice. The basis of proper management of these ailments is essentially restoration of normal intestinal activity. The best confirmation of the decisive role played in the etiology and pathogenesis of sprue by the state of the intestines is derived from the simple fact that normalisation of intestinal activity usually leads to recovery from sprue: the anemia disappears, the endocrine functions are restored, as are the patient's somatic well-being, his weight, etc.

What is most important in the proper treatment of sprue and of fermentative enteritis is a special antifermentation diet. In general, our experience has shown that chronic enterocolitis developing on the basis of fermentative enteritis best responds to an antifermentation diet. The prescription of such a diet proves to be the best therapeutic measure in the majority of cases. We hold that the unreasonable treatment so frequently adopted for acute and protracted enteritis and enterocolitis, and for acute fermentative dyspepsias of childhood—all of which are prominent in the pathology of hot climates—is an unhappy misunderstanding; the patients are given a so-called light diet of dairy products, but this light diet, as we have on numerous occasions observed, leads to grave results: the patients degrade and finally succumb. On the other hand, consecutive observation of the principles of antifermentation diet evolved by A. N. Kryukov's school invariably has an amazingly good effect.

A strict protein-fat diet containing enough calories is prescribed. Its approximate composition: as many as 6 eggs a day, up to 50 g of fresh butter, 400 g of boiled forced-meat balls, boiled fish (instead of meat), fresh (with no trace of sourness) curds (up to 200 g), fresh cream, walnuts (10-15 nuts a day). Fruit juices should be given with caution, as they may promote intensification of the fermentative processes. Pomegranate juice is positively beneficial as it contains astringent substances, and the same is true of the dried fruit of the plant *Elagnus hortensis* of which 100-150 g (peeled) is given per day. Vitamins are best offered in the form of concentrates or tablets. All farinaceous foods, bread, toast, milk, sugar, potatoes, fresh fruits and vegetables are absolutely excluded. Only after the patient starts passing normally formed alkaline stools is his diet gradually extended to contain carbohydrates (beginning with very small amounts): vegetable puree, porridges, toast, sugar, and fruit (but no milk!).

Diet therapy is combined with intravenous injections of 10 per cent calcium chloride, 10 ml a day (20-30 injections in all). Calcium is also given by mouth in the form of Calcium carbonicum,  $\frac{1}{4}$  teaspoonful 3-4 times a day, or by the following prescription:

Rp.   Acidi nicotini   0.02  
      Calcii carbonici 1.5  
      Dermatoli       0.4  
      M. D. t. d. No. 30  
      S. 1 powder 3 times a day before meals

It is also advisable, in consideration of parathyroid dysfunction, to give daily subcutaneous injections of 1 ml of parathyriocrin (parathyroid extract) to promote calcium assimilation. Pancreatic preparations are given by mouth—pancreatin or pancreon (a Soviet preparation similar to pancreatin) 1 g 3 times a day; natural gastric juice or hydrochloric acid with pepsin are given for achylia. A 50 per cent infusion of pomegranate rind (*Inf. Corticus fructus granati*, 50%), 10 tablespoonfuls per day, is also recommended.

Particular stress should be laid on the treatment of anemia caused by sprue, all the more so as such treatment yields a general therapeutic effect and benefits intestinal reparation.

Currently excellent results are obtained in the treatment of sprue with vitamin B<sub>12</sub> injections; 30 to 100 mg are given on alternate days, 15-20 injections in all. If we take into consideration that folic (pteroylglutamic) acid is associated with vitamin B<sub>12</sub> and the whole intricate vitamin B complex, deficiencies of which are particularly marked in the pathogenesis and clinical features of sprue, we shall understand why sprue patients also need folic acid. Our personal observations, as well as those of B. P. Shvedsky (Tashkent) and I. B. Likhtziyer (Dushanbeh), show that this preparation is highly effective in the therapy of sprue and concomitant anemia. Patients are given large doses of folic acid—0.1 g 2-3 times a day for 2-3 weeks.

Two other therapeutic factors are highly important in treatment of severe forms of sprue—endocrine preparations and blood transfusions (whole blood or packed erythrocytes).

The endocrine preparations of choice are cortisone (50 to 100 mg), cortin, pituitrin; for pronounced symptoms of diabetes insipidus the patient is given pulverised desiccated posterior pituitary for inhalation (*adiurecrinum*, *pituitarium posterius*, *hypophysis sicca*), etc. The transfusion of whole blood or packed erythrocytes is a powerful therapeutic factor for counteracting emaciation and persistent intestinal disturbances. No less than 5-6 transfusions must be done, allowing 150-200 ml of whole blood or 100-150 ml of packed erythrocytes per transfusion. Transfusions have a good general effect on the system and on blood formation, and they promote reparative processes in the intestines.

Finally the effect of the hot atmosphere per se on the origin of sprue and fermentative diarrhea must also be considered. Personal experience has shown the authors (who have worked for considerable time in warm climate zones) that it is not uncommon for remissions to be rapidly followed by relapses. The morbid condition then best responds to treatment in areas where the climate is more temperate, and to which the patient is advised to remove for a long stay during the summer heat.



# BERIBERI

---

Synonyms: athiaminosis, kakke, barbiars, and other local names. This is a morbid condition due to vitamin B<sub>1</sub> deficiency. Its classic clinical syndrome consists of polyneuritis, edema, heart failure. The disease is common to south-eastern Asia.

Currently two clinical forms of the disease have been distinguished; they are recognised under the terms of B<sub>1</sub>-hypovitaminosis and beriberi. The latter is a severe form of protracted vitamin B<sub>1</sub> deficiency associated with the food habits of southern lands, and also with the effect of heat.

The name of the disease in different languages originates in its cardinal symptom — polyneuritis characterised by weakness of the legs.

## HISTORICAL DATA

Beriberi is a disease that has been known since ancient times. It is mentioned in writings dating back to the 2nd century A. D. (data communicated by the Japanese doctors Kambeh and Ioshida). The Chinese book "Sen-kin-ho" (8th century) contains a detailed description of the clinical features of beriberi. The first comprehensive scientific description of beriberi, as well as the proper recognition of the leading part played by dietary deficiency in the onset of this disease, were made by a Japanese naval doctor, Takachi, in 1884. By providing food of full dietary value (meat, fish, vegetables, barley) he succeeded in lowering the beriberi rate from 30-40 per cent to 0.5 per cent in the Japanese navy (which had previously been limited to rice rations).

A Dutch doctor, Eikman, working on Java in 1897, described polyneuritis in chickens whose feed consisted mainly of polished rice.

## GEOGRAPHICAL DISTRIBUTION

Beriberi is predominantly a disease of east and south-east Asia, where the staple food is rice: Japan, the Korean People's Democratic Republic, South Korea, South China, India, Thailand, Cambodia, Viet-Nam, Indonesia, Ceylon. On Soviet territory beriberi is encountered in Central Asia, where it was first comprehensively described by I. A. Kassirsky (1933).

## ETIOLOGY

After the teachings on vitamins had become firmly established (N. I. Lunin, Funk) a series of investigations devoted to clarifying the chemical nature of vitamin B<sub>1</sub> and its isolation in pure form were undertaken as early as 1911-13. In 1912, an active antineuritic vitamin — orizanine — was recovered from rice bran; several milligrams of this preparation cured pigeons of experimental beriberi. Soon afterwards a similar preparation was obtained from yeast. Susuki, Funk, Jansen, and Donath obtained vitamin B<sub>1</sub> in crystalline form from yeast and rice bran. All these substances invariably cured experimental polyneuritis. However, a chemically pure form of vitamin B<sub>1</sub> was only obtained in the 1920's, when it was recovered from the water-soluble vitamin B contained in yeast, rice hulls, etc.

Contemporary experimental data has proved that vitamin B<sub>1</sub> is essential for the realisation of the trophic function of the nervous system, as it provides normal conditions for the physico-chemical processes occurring in the nervous tissue (S. M. Ryss, 1955).

Vitamin B<sub>1</sub> stimulates the metabolism of mediators, thus participating in the complex mechanism of nerve stimulation.

It has also been established that vitamin B<sub>1</sub> has a specific regulating effect on pyruvic acid metabolism.

Together with pyridoxine vitamin B<sub>1</sub> participates in the conversion of protein to fat.

Vitamin B<sub>1</sub> also has a specific effect on the cardiovascular system via vegetative and trophic regulation; consequently, lack or absence of this vitamin (hypo- or avitaminosis) results in grave circulatory disturbances: heart failure, i. e., slowing down of the velocity of circulation, decreased tonicity of the arterial system (M. S. Belonogova-Lang).

## CLINICAL ASPECTS

Long-term observations made by the authors have led them to the conclusion that beriberi is a complex and manifold clinical syndrome with a highly mobile symptomatology. They consequently support the most widespread classification of beriberi, wherein the existence of various forms and patterns of the disease is accepted (S. M. Ryss): 1) the rudimentary form (B<sub>1</sub>-hypovitaminosis); 2) the dry atrophic form; 3) the edematous form; 4) the acute pernicious form.

*Acute* and *chronic* courses of beriberi are distinguished.

Pernicious beriberi (called "shoshin" by the Japanese) is a specific aspect of the acute form, associated with a prevalence of severe cardiovascular disturbances with fatal termination.

During recent decades another acute form of the disease — ship beriberi (Segelschiff beriberi) has been identified as exhibiting certain specific features.

Chronic beriberi is usually subdivided into the following forms: 1) the *edematous* form, 2) the *cachexial* form, and 3) the *late cachexial form with edema*.

The principal features of the clinical syndrome of beriberi are neural and cardiovascular disorders, profound disturbances of protein, fat, fluid and electrolyte metabolism, and dystrophic changes in the organs.

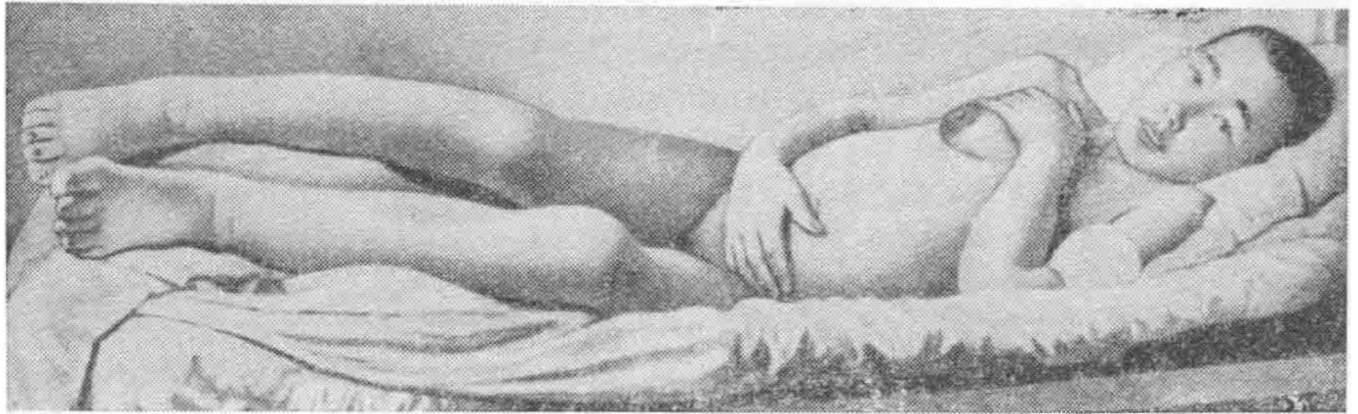


Fig. 128. Beriberi patient

The *neurologic symptomatology* is basically manifested by the development of a specific type of neuritis with a very gradual onset that first affects the sensory nerves. The first symptoms of the disease are paresthesia of the legs and feet and of the outer aspects of the feet and toes. Later a diminution of the sensory responses in the sock or stocking region is noted, a condition that in rare instances develops into anesthesia. Gradually the area involved in paresthesia and hyposthesia expands, spreading in rare cases over the entire surface of the body. Unaffected areas usually remain around the eyes, in the nape of the neck, on the inner aspects of the thighs, and on the soles. Commonly all three types of sensibility are affected, even deep sensibility; this is expressed by an ataxic syndrome.

A marked symptom of beriberi is muscular pain, particularly in the lower extremities.

Lesion of the motor sphere is usually simultaneous with lesion of the sensory sphere. It is manifested by a sensation of weakness and insuperable heaviness in the legs; walking becomes difficult. Pareses soon develop, predominantly in the extensor muscles of the feet. In progressive cases the pareses develop into paralyses involving all the muscles of the lower extremities, and this in its turn is followed by muscular atrophy.

Lesion of the extensor and lateral peroneal muscles were present in the majority of patients the authors have observed.

As the lesions of the lower extremities deepen the gait of the patient changes, as does the position of his legs and feet when he is recumbent or sitting (Fig. 128). In walking the feet are spread as if for widening the support of the trunk, the gait is of the tripod type (*marche en trépied* of the French authors), or it becomes noticeably ataxic (*pseudotabes beriberique*). If lesion of the peroneal groups of muscles occurs then foot-drop is seen; lesion of the iliopsoas muscles is manifested by the inability of the patient

to lift his legs or cross them, in a sitting position, without the aid of his hands. In rare cases the neuritis spreads to the upper extremities; involvement of the cranial nerves is extremely uncommon.

*Cardiovascular syndrome.* Cardiovascular involvement in beriberi is of the most diverse nature, ranging from mild signs of pulse lability to severe circulatory failure. In some cases no marked cardiovascular symptoms are observed, but this does not exclude the diagnosis of beriberi. It is possible that the onset of cardiovascular failure requires some additional disturbances in protein and specifically vitamin metabolism. Moreover, another important point is that the hypoproteinemic edema concomitant with beriberi may likewise create an "additional" impression of cardiac edema.

The clinical features of classic lesions of the cardiovascular system in beriberi have been described by Wenckebach and his associates (1932-34). In mild forms or at the onset of the disease heart palpitations, dyspnea, and at times a slight swelling of the feet and legs are noted. The pulse is irregular, and this is particularly noticeable in various types of functional stress. Skiagraphy occasionally shows distention of the heart to the right.

*Moderate and severe forms of beriberi* are characterised by pronounced neural symptomatology and general disorders (edema, cachexia). Patients complain of heart palpitations and of a peculiar sensation of "beats in the heart". Palpation reveals a lifting pulsation of the heart, predominantly due to the right ventricle—left and right of the sternum and under the xiphoid process. The contours of heart are enlarged, mainly to the right, to a lesser extent to the left. Auscultation elicits dull sounds and a systolic murmur at the apex of the heart.

Slight stasis is noted in the lungs, sometimes hydrothorax is observed. The liver is usually enlarged, the patients often experience pain in the right subcostal region.

Cardiovascular and general symptoms are particularly pronounced in the fulminant form of beriberi—the Japanese "shoshin" (meaning "heart attack"), or the *forme foundroyante* (fulminating form) of French specialists in tropical diseases.

The principal findings in "shoshin" are pains in the chest resembling angina pectoris, perception of the heart beats, accelerated, shallow respiration (approaching 40 times per minute), pulse rate as high as 130 beats per minute. Patients are usually weak, restless (some extent of psychomotor excitation is noted), their lips and extremities are cyanotic.

Thus we see that the entire symptom-complex resembles the picture seen in diphtherial affections of the heart.

The ECG usually indicates some shortening of the interval between *P* and *Q*, decreased voltage, and a lower *T* peak in the first and second standard leads.

Wenckebach, who made a most circumstantial study of blood circulation in beriberi patients, pointed out the presence of dilatation of the heart in this sickness; most dilated is the right heart, coupled with venous stasis in peripheral circulation. The Olsmeer test with introduction of 1 ml of adrenalin subcutaneously produces a decrease in arterial pressure and

simultaneous increase in venous pressure. Quite the opposite is attained by the injection of an extract of the posterior lobe of the pituitary—increased blood pressure in the arterial system and decreased pressure in the venous system.

In Wenckebach's opinion the cardiac syndrome of beriberi depends on the concurrence of two factors: sharp degenerative changes in the myocardium, leading to cardiac failure, and dilatation of the finest branches of the peripheral arteries accompanied by influx and accumulation of blood in the venous system, liver and right heart. Clinical observations of their patients have shown the authors that the reaction to the adrenalin test corresponds to that cited by Wenckebach, while the heart is acutely affected, as manifested by its dilatation, dull sounds, the ECG and patho-anatomic changes.

Blood system findings are anemia, not very marked, of the hypochromatic type, less frequently—a more pronounced anemia, with a normal white blood count and slight increases of the lymphocytes in the differential white count. The ESR is accelerated. The ascitic fluid is of the transudative type, with a low protein content.

*Ship beriberi*—beriberi of the sailing fleet. This form is proof of the possibility of mild, asymptomatic forms of the disease developing on the European continent and in the western Asiatic countries (personal observations in Central Asia).

Ship beriberi appeared in the 1890's in association with changes in ship rations (salt pork was replaced by tinned meat, brown bread by white, the crews were given less legumes). In this form of beriberi weakness and paresthesia of the lower extremities also develop, but the paresis symptoms are much less marked; the cardiovascular symptoms are likewise not so pronounced as in rice beriberi.

## PATHOGENESIS

The connection of beriberi with vitamin B<sub>1</sub> deficiency is beyond any doubt whatsoever; however, it is only natural that no complete analogy can be drawn between experimental beriberi in birds and beriberi in man with his complex nutrition. As has now been established experimentally, and as the present authors have observed during their long-term clinical studies in Central Asia, vitamin deficiencies in man, even in conditions of starvation, cannot develop as an isolated experimental avitaminosis does.

As early as 1922 (when there was yet no precise delimitation between the different vitamin B fractions), L. A. Cherkes revealed that the group of B vitamins was directly connected with protein metabolism; this connection was defined by the presence of these vitamins in the active group of certain enzymes of nitrogenous metabolism, some of them being directly responsible for enzymatic reactions, others being indirectly connected with protein metabolism. Subsequently O. Y. Parnas, A. Y. Braunstein, M. G. Kritzman specified the precise mechanism of this participation of vitamins in protein metabolism. They found, for instance, that vitamin B<sub>1</sub> participates

in the transamination of amino acids, i.e., in the intermolecular transposition of the amino group and hydrogen of glutamic acid into pyruvic acid, a process that maintains and enacts the complex amino acid exchange in the muscles and liver.

In beriberi the vitamin B<sub>1</sub> deficiency is accompanied by marked protein hunger, and this is the principal cause of intensification of the edematous or cachectic features of the disease, with dystrophic changes in the organs.

This point is confirmed by the experimental and clinical findings in man reported by Williams, Wilder, and Smith (1946) (cited from S. M. Ryss, 1955).

A number of auxiliary factors promote the development of the classical picture of beriberi—first and foremost among them are disturbances of protein nutrition and the effect of hot atmospheres; the development of beriberi of Eastern Asia (Japan, China) follows a prolonged diet of polished rice and sharply decreased protein nutrition.

As the authors have seen in Central Asia, it is not uncommon for beriberi to be joined by other vitamin deficiencies, such as scurvy, pellagra, and sprue (polyavitaminosis).

### PROGNOSIS

Prognosis depends on the form of the disease and its stage. In mild initial forms prognosis is favourable; in advanced forms accompanied by severe edema or cachexia, and also in fulminating forms prognosis is grave; it is particularly grave for pronounced cardiovascular disorders.

### TREATMENT

In all cases treatment consists first of all of providing the patient with food of full dietary value (proteins, fats, carbohydrates and vitamins). Vitamin B<sub>1</sub> is given parenterally in large doses, 40-50 mg per day, in two portions. The large doses are administered for one or two weeks, and then the patient is given 20-30 mg daily for 2-3 months. Upon marked improvement vitamin B<sub>1</sub> may be given perorally instead of parenterally.

Rp. Thiamini bromati 5% 1.0  
D. t. d. No. 10 in amp.  
S. For injections of 0.5 ml.

Rp. Thiamini bromati 0.01  
Sacchari 0.3  
M. f. pulv. D. t. d. No. 12  
S. 1 powder 2-3 times a day

In so far as polyavitaminosis symptoms are observed in beriberi it is advisable to prescribe other vitamins too:

Rp. Acidi nicotini 0.025  
Riboflavini 0.003  
Acidi ascorbinici 0.15  
Glucosae 0.5  
M. f. pulv. D. t. d. No. 20  
S. 3 powders a day

Cardiovascular disturbances are treated with digitalis.

Rp. Pulvis fol. Digitalis 0.03  
Theobromini 0.2  
Calcii gluconici 0.5  
M. f. pulv. D. t. d. No. 20  
S. 3 powders a day.

To decrease the edema euphylline (theophylline ethylenediamine or aminophylline) is given by clysis (0.3-0.4 g); ten hours later a mercusal injection may be given (mercusal is a Soviet preparation similar to mercuzanthin or mercurphylline injection). The tonus of the nervous system and cardiac muscle is improved by injections of strychnine (1:1,000 solution, 1-1.5 ml per injection).

Bed-rest is essential during the period of edema and adynamia. Upon recovery of strength and disappearance of general dystrophic disorders massage is prescribed for the legs and feet, also therapeutic exercises, physical therapy. In severe cases recovery is extremely slow.

# ALIMENTARY TOXICOSIS

---

Alimentary toxicosis is a condition observed in tropical and subtropical countries owing to the consumption of various poisonous grains, weeds, etc.

## HELIOTROPE HEPATITIS (HELIOTROPE DISEASE)

Heliotrope hepatitis is a peculiar disease characterised by far-reaching degenerative processes in the liver and other organs as a result of toxicosis caused by the consumption of the seeds of plants of the heliotrope family.

### Historical data

The first communications on familial morbidity and small outbreaks of the heliotrope disease were made about 40 years ago by a rural general practitioner, Dr. Spiridonov.

Subsequently detailed clinical descriptions of the disease were published by M. F. Mirochnik (1931), G. N. Mirzoyan (1933), and A. N. Ivanov (incidence in children, 1933); however, the etiologic factors were for a long time unknown. The first researcher to point out the role of heliotrope plants in the development of the disease was H. H. Tzenner (1945). This author affirmed that the wheat crops were contaminated by heliotrope weeds that grew abundantly in the fields, and that these heliotrope weeds were the cause of the poisoning. Tzenner carried out a number of experimental investigations, feeding chickens with bread and flour containing heliotrope seeds and then establishing morbid changes in their organs.

Subsequently complete experimental confirmation of the part played by heliotrope plants in the onset of hepatitis with ascites was established by M. N. Khanin (1940-56), who carried out a cycle of classic investigations. S. B. Dubrovinsky investigated the sanitary and hygiene conditions of the population, confirming the hypothesis set forth by H. H. Tzenner and M. N. Khanin (1947). The subsequent experimental and clinical in-



vestigations of a number of authors performed in the 1945-55 period (N. N. Kompantsev and G. V. Burkser, G. N. Terekhov, A. S. Sadykov, S. Y. Yunusov, N. I. Ismailov, etc.) clarified the crucial problems in the etiology, pathogenesis, and clinical features of the heliotrope disease.

### Geographical distribution

Heliotrope hepatitis is common to the republics of Central Asia — Uzbekistan, Tajikistan, Turkmenistan, Kirghizia, and some areas of Kazakhstan, to Armenia, Azerbaijan, and also to Afghanistan, Iran, India, and some other countries. The malady also afflicts poultry fed with bitter (heliotrope) flour or chopped grain.

### Etiology

Although quite a number of plants contain hepatotoxic alkaloids, still the largest amount is to be found in representatives of the genera *Senecio*, *Crotalaria*, and also in *Heliotropium lasiocarpum*. There are over 220 species of heliotropes (called tuya-karin in the Uzbek language); over ten species grow in the Central Asia republics. The heliotrope *Heliotropium lasiocarpum* is an annual plant; the height of its stem, which grows out into a branching shrub, is 20-40 cm, sometimes even more. The leaves are oval-shaped, and many small white or purplish flowers grow on the shrub. The small (3 mm) fruit is tetrahedral; when ripe it readily splits into four little nuts, each one containing seeds. The plant produces up to 4,000 seeds in one season. Both the shrub itself and its seeds contain powerful hepatotoxic alkaloids — heliotrin and lasiocarpine; the content of these substances is much higher in the seeds than in the other parts of the plant, and it is namely the seeds that contaminate the crops of wheat, barley, millet, joughara (a species of sorghum), mash (a leguminous plant), and other cultures. A daily ingestion of 2 g of seeds per kg of body weight for a period of 20-30 days is fatal to dogs, while 0.4 g ingested daily for six months brings on chronic toxicosis. N. N. Kompantsev (1947) established the toxicity of heliotrope alkaloids on a number of birds. At the same time histomorphological examinations of animal organs demonstrated specific lesions of the parenchymal cells and vessels of the liver. In experimental animals the disease appeared in both the acute and chronic forms. The acute form showed necrotic changes and hemorrhages in the hepatic cells; in the chronic form destruction of the hepatic cells and cirrhosis occurred.

### Clinical aspects

The clinical pattern of the heliotrope disease is divided into four periods: 1) pre-ascitic; 2) ascitic; 3) reparative; 4) cirrhotic.

The incubation period depends on the amount of toxin that was ingested, the period of time over which it was taken, and also individual reactivity. In some patients prodromal and pre-ascitic symptoms are ob-

served soon after the consumption of bitter bread (within 5-7 days), while others state that they had been having bitter bread regularly for one or two months before feeling the first symptoms of the disease.

Principal clinical and morphologic symptoms of heliotrope disease are lesions of the liver.

The first signs are pain and a sensation of distention in the right subcostal area; then dyspeptic symptoms (loss of appetite, nausea), and periodic diarrhea appear. In many cases a rise in temperature is noted (37.5-38.8 °C). All symptoms are more acute in children, and the development of the disease is more rapid in them. Enlargement of the liver and some small degree of jaundice are noted at this stage of the disease.

The duration of the pre-ascitic period varies: ascites does not develop in some patients whose bread was not very bitter, and who did not have it too often, while in others it may appear within a month or two. Commonly the ascites appears 2-3 weeks after the onset of the disease.

Findings most characteristic of the ascitic period are increasing hepatomegaly; the lower edge of the liver protrudes 5-6 cm below the subcostal ridge. The authors have, as a rule, observed density of the liver and some yellowness of the skin. Dyspeptic signs are periodic. Predominant among them are nausea and vomiting, the vomitus may contain blood. Loss of strength and emaciation develop rapidly. The skin is dry, exfoliative, yellowish-grey.

In a number of cases the ascites very soon (within a matter of 5-6 days) attains large dimensions, in other cases its accumulation takes several weeks. The ascites is often amazingly large, calling for repeated punctures (8-12) to evacuate the fluid. Moderately dilated veins are seen on the abdominal skin. The ascitic fluid has a relatively low protein level and a low albumino-globulinic index.

The liver enlarges gradually; such enlargement at the commencement of the disease is a favourable sign. Reduction of the liver concomitant with aggravation of the patient's condition is a sign warning of the danger of the development of hepatargia and coma — grave prognostic signs.

A gradual reduction of the liver in the process of recovery is a favourable sign.

Spleen enlargement is usually only slight.

Other symptoms worth mentioning here are myocardial dystrophy with a lowered voltage on the peaks of the ECG, and lowered arterial pressure, also nephropathy (heliotropic nephropathy); neuropsychic findings in such cases include psychomotor excitation that is later replaced by apathy. The temperature is commonly irregularly subfebrile.

Sometimes a condensation of the blood is observed during the period of ascitic growth (hypercytemic hypovolemia), increased hemoglobin values and erythrocyte counts, subsequently anemia. There are no characteristic changes in the white blood. Decrease of the total protein value is attended by some increase of the globulin fraction. Sugar tests show an inhibition of the glycogen function of the liver, Quick's hippuric acid test shows the antitoxic function of the liver to be depressed (N. I. Ismailov,

1948). Bilirubinemia is no greater than 1-1.8 mg% (direct bilirubin, slow-ered reaction). During the reparative period all the above symptoms gradu-ally subside: the liver returns to its normal size, the ascites disappears, the patient regains his strength.

The course of the disease depends on its form. In mild cases, partic-ularly in the absence of ascites, complete recovery is effected: normal liver and complete restoration of its functions. In cases of moderate severi-ty recovery is complete in only 40 per cent of patients, while in the other 60 per cent residual hepatitis develops, subsequently leading to cirrhosis of the liver. In severe forms either hepatargia, terminating fatally, occurs, or the patients succumb in the ascitic period, showing symptoms of general emaciation, or else the disease runs on for a very protracted period of time and ends in cirrhosis of the liver.

### **Treatment**

The most effective method of treatment is insulin-glucose therapy (intravenous injections of glucose are given 1-3 times a day with 5-10 units of insulin depending on the severity of the disease).

To counteract the ascites mercusalootherapy is recommended: 0.3-0.4 g of euphylline (aminophylline) is given by clysis over a period of 8 hours, and then 0.5 ml of mercusal (mercuzanthin, mercurophylline injection) is injected. These injections are repeated once in three days. A too frequent evacuation of the ascitic fluid by paracentesis is undesirable, as it leads to emaciation, and therefore mercusalootherapy is indicated; however, the mercusal dosage and frequency of injection should be restricted, as this preparation has a toxic effect on the hepatic parenchyma.

In addition to the above, it is recommended to give patients lipocain (0.1 g 3 times a day) and methionine (0.5 g 3 times a day) for prolonged periods.

Food of full dietary value should be given. First of all the patient must be provided with full-value carbohydrate and vitamin nutrition. Ascorbic acid is particularly recommended (0.25 g 3 times a day); injections of vitamin B<sub>12</sub> (30 micrograms) are given every other day, 15 injections in all. At the same time it must not be forgotten that symptoms of protein deficien-cy are often present in the heliotrope disease, aggravating the course of the hepatitis (hepatitis in alimentary dystrophy has been described). Therefore it is important to give patients full-value proteins (without overburdening): curds, boiled meat, boiled fish; the fats recommended are fresh butter and fresh cream in moderation.

### **Prophylaxis**

The basic means of avoiding heliotrope poisoning are proper manage-ment of grain cleansing, obligatory separation of the heliotrope seeds from the grain through sieves with 1.5-mm grid cells, observation of certain

agrotechnical rules, and sanitary education of the population (warning of the danger of consuming bitter flour or bread). In cases of ingestion of toxic bread the measures recommended are gastric lavage, cathartics, and early therapy. Alcohol in any form is forbidden, as it is conducive to hepatitis.

## EFFECT OF WARM CLIMATE ON THE HUMAN BODY

---

Heat is the most important of the climatic factors of warm lands that affect the human system. The thermal equilibrium of the body is maintained at a definite level, notwithstanding oscillation in environmental temperature. "The perfection of the human higher nervous activity and the high degree to which thermoregulation has developed have made it possible for man to master all the climatic zones of the globe, including the tropics, the Arctic and Antarctic regions" (N. V. Danilov).

Some authors erroneously speak of the essentially harmful effect of warm climates per se on the human body. The effect of climate is very complex, manifold and dynamic: some factors have a positive effect on the human system, others a negative effect (e.g., an excessive environmental heat attended by increased humidity may cause hyperpyrexia even in people accustomed to heat). However, a proper approach to the problem of the effect of climate on the human body must be made from the standpoint of physiological adaptation, so-called acclimatisation.

*Acclimatisation* is an intricate social and biological process, the most prominent features of which are the development of physiologic adaptation and the active process of the creation of a socially-organised environment adapted for work and life in local climatic conditions (L. Matz, A. N. Sysin, et al.). Evidently, acclimatisation (adaptation to climate) can only be successful if other factors, dependent on social conditions, participate, such as housing, air-conditioning, special clothing, food.

Practice has proved that man gradually adapts himself to any climate. The adaptative physiological reactions are very complex. They are based on reflex mechanisms mobilised by the effects of cold or heat.

Naturally, in the phylogenetic aspect man is more adapted to warmth than to cold; adaptation to cold is much more complicated in the animal kingdom, including man, too (fur, warm clothing).

The present chapter dwells on the effect of the heat factor on the human body.

It is commonly known that any animate system affected by warmth dissipates warmth into its surroundings. When a certain balance is maintained between these two opposite but physiologically united processes the body temperature remains stable. Should human heat dissipation be stopped for two hours the temperature would go up 3-4°C.

The routes of heat dissipation vary. The skin is responsible for up to 80 per cent of heat losses. The skin dissipates warmth by convection, by radiation, and by the evaporation of sweat. When the environmental temperature exceeds that of the skin the most efficient method of heat dissipation is the evaporation of water on the surface of the skin. The system uses up 580 calories for evaporating one litre of water. The secretion of sweat is the basic process in the physiology of heat dissipation. A person walking with a speed of 5.5 km/h in the heat of the sun, when the atmospheric temperature is 32.2 °C, excretes 750 ml of sweat in one hour; whilst working hard in similar conditions he may lose as much as 10 litres of fluid (N. V. Danilov, 1956).

However, neural regulation of the processes of heat generation and dissipation generally maintains the temperature of the human body within a normal range of 36 to 37 °C. N. Y. Kuznetsov, after taking 3,500 body temperature measurements during the summer heat in Tashkent, concluded that the human temperature remains within normal limits. However, working in the Kara-Kum desert, where environmental temperatures were higher, Kuznetsov found that the human temperatures rose to 37.5 °C. Heat adaptation may be impaired by the following causes:

- 1) intensification of the heat (thermal) factor;
- 2) inadaptability of an individual accustomed to another climate;
- 3) dysadaptation due to the individual state of the system or its morbidity;
- 4) physical over-exertion and inadequate clothing, housing, and certain other conditions.

Under the effect of heat physical (and to some extent chemical) thermoregulation becomes active. Physical thermoregulation intensifies heat dissipation, while chemical thermoregulation lowers its generation. Both processes are simultaneous, but in hot environments chemical thermoregulation is not as powerful a factor as physical thermoregulation.

Climatic factors are extremely variegated, as are their effects on the human body. Man is capable of withstanding an environmental temperature of 80 °C in dry air, but 32° C becomes intolerable in humid air (Starling). The highest limits of human thermoregulation are considered 30-31° at a relatively high humidity (85 per cent) and 40° at low humidity.

The thermoregulating mechanisms are less active in dry heat, while heat associated with a high relative humidity (as in the tropics) calls for intensive thermoregulation: already at 29 °C heat dissipation by evaporation increases from 12 to 70 per cent (Borchardt). At 34° dissipation of heat via conduction and radiation sharply decreases, and the prevailing

mechanism is that of evaporation. As the environmental humidity increases the air absorbs less water and heat, and physical thermoregulation becomes impaired; the result is overheating—hyperpyrexia.

A special expedition to desert areas sponsored by Harvard University established that the ability of various individuals to withstand the effects of hot climates depended to a great extent on the facility of sweat secretion. The criterion of ideal tolerance to hot atmospheres are free sweat secretion and general good health; in this respect the showings of acclimated or hardy individuals are good. I. A. Kassirsky and Y. V. Poslavsky (1931), V. K. Solovyov (1933), G. I. Samokhin (1936), and other authors working in Tashkent and Khorezm established that fluid metabolism in the quiescent state comprises 3 litres on the hottest days, and about 6 litres when the subject is engaged in physical work. This is accompanied by the intake of as much as 6 litres of water a day and the evacuation of 300-400 ml of water with the urine and 5 litres with the sweat.

### HEAT HYPERPYREXIA

Synonyms: diathermasia, hyperthermic disease, thermic fever, sunstroke (inaccurate definition), heat stroke; the terms most commonly used are the English terms: heat hyperpyrexia, heat pyrexia, thermic fever, insolation, heat stroke, sunstroke.

Definition: a hyperpyrexial response of the body as a result of impaired thermoregulation in conditions of excessive heat existing in hot climates or overheated premises (foundry-works, etc.).

Currently no specific distinction is made between heat stroke and sunstroke.

### Pathophysiology and pathogenesis

The excessive heat supplied by the environment, coupled with impaired heat dissipation, results in hyperpyrexia in persons with faulty neural regulation of the metabolic processes; the extreme form of this hyperpyrexia is heat hyperpyrexia or heat stroke. When the exposure to excessive heat occurs in direct sunlight it is called *sunstroke*. At present it has been found that the clinical features and pathophysiologic mechanisms of sunstroke and heat stroke are one and the same, therefore they are not differentiated as two nosologic forms (F. G. Krotkov, 1948; N. V. Danilov, 1956).

Factors conducive to heat pyrexia are a high environmental temperature with sharply increased humidity in the absence of air movement; heavy physical work; thick, tight clothing; high protein diet, and insufficient elimination of water through the skin.

Heat strokes are most frequent among inadapted newcomers in tropical or southern countries. The thermoregulating systems of such individuals are subject to overexertion. Aggravating conditions promoting the development of the hyperpyrexial syndrome are, first of all, protracted exposure

to the sun or to heat in stuffy, closed premises, prolonged physical exertions (particularly long military marches and walking-tours the participants of which are not adapted to the climate).

F. G. Krotkov (1948) pointed out that the intensified muscular activity associated with walking 120-130 steps per minute causes the temperature of the body to rise 1-1.5°C. Walking with a load weighing 22-31 kg makes the average body temperature rise to 37.3-38°C. (F. G. Krotkov). Forced marches increase heat generation ninefold. In such conditions heat dissipation by radiation and conduction is stopped, and the only route is through perspiration. Obstruction of the latter by high humidity, tight or heavy clothing is a frequent cause of hyperpyrexia and heat stroke. Hygienic rules for warm lands have been adequately worked out to date; these rules include a number of efficient solutions of the problem of hyperpyrexia in warm climates. Formerly negligence of proper prophylactic measures resulted in a high incidence of sunstroke casualties among soldiers. Thus, during the 1839 Algerian expedition 200 French soldiers were incapacitated within several hours, 11 of them died. In an American regiment numbering 1,200 men 25 per cent fell out of the ranks during a forced march on Pekin in 1899. In the period between March 26 and July 14, 1873, the Russian Krasnovodsk detachment, moving through the Karakum desert to Khiva, registered 107 heat strokes among its 2,165 men; however, the actual figures were probably still higher, as another report on this expedition says that something like 100 mounted Cossacks and 100 foot-soldiers were prostrated with sunstroke and had to be tied to the camels.

Diseases like malaria, pappataci fever, dengue, and other hyperthermic ailments, as well as alcohol intoxication and dystonia of the autonomic nervous system, are also conducive to the development of a heat stroke. Local inhabitants of hot lands are affected by hyperpyrexia to a much lesser extent.

### **Clinical aspects**

Heat hyperpyrexia is characterised by variegated clinical features that depend both on the patient's reactivity and the stage of the morbid condition. Symptoms of heat stroke appear during the period of maximum insolation, but at times they display themselves only after the patient has left the zone of insolation and is resting in the shade. If the patient is removed from the zone of excessive heat in the prodromal or initial stage of the condition and urgent first aid measures are taken, the reaction may be limited to syncope, a sensation of stuffiness, weakness, and either a slight elevation or decrease of the temperature; the pupils are dilated, respiration is shallow. In moderate and severe cases all symptoms increase quite rapidly. Repeated syncope accompanied by paroxysms of acute weakness are followed by severe headache, a sensation of deafness, weakness in the lower extremities, uncertain movements, tachycardia, somnolence, nausea, quickened and superficial breathing, sensations of compression in the chest. The skin is dry, the volume of urine passed decreases; other findings are



photophobia, hyperemic conjunctiva, contracted pupils, flushed face. Blood tests show a decrease of chloride, calcium, and sodium ions.

Subsequent developments are the appearance of severe neurological symptoms: intensified headache, excitability, frequently delirium (in 25 per cent of cases), muscular cramps; respiration becomes shallow, accelerated, irregular. The temperature goes up to 39, 41 and even 42°C.

The patient becomes unconscious, his pupils dilate and do not react to light, the pulse is small and thready, peripheral blood circulation slows down; the skin becomes dry and hot, or it is covered with a profuse clammy sweat; the face, flushed at first, now takes on a pallid cyanotic hue; bowel incontinence is observed, the tendon and abdominal reflexes are lowered or absent; urinalysis frequently reveals albuminuria.

Several forms of the disease have been described, in accordance with the prevailing symptoms: *cardiovascular, pulmonary (atelectasis), cerebral, shock, and delirious* forms.

Severe forms terminate fatally.

### Prognosis

Prognosis depends on the stage and form of the condition. Heat strokes are fatal in 5 to 15 per cent of cases. When conditions are very difficult (military marches when the soldiers are exhausted by disease or hunger) the mortality rate is much higher—up to 20 or 30 per cent. Recovery is very slow.

### Pathology

The pathological findings are not always characteristic, therefore post-mortem diagnosis is often established on the basis of anamnestic data (F. G. Krotkov). Autopsy shows the presence of liquid blood due to asphyxia, hyperemia of the soft meninges of the brain, pinpoint hemorrhages in the brain. Parenchymatous degeneration is evident in all the organs. The lungs are congested with dark liquid blood.

### Prophylaxis

Prophylactic measures are essential, and when they are properly managed heat strokes are usually avoided. These measures are defined by the concrete conditions. Soldiers on the march or foot-travellers are advised to walk in open ranks with unbuttoned collars, and to rest frequently in cool, shady places; drinking water should be available, and special drinking cycles instituted; recommended drinks are acidified tea, strong tea, rice water, and fermented drinks such as Russian kvass (a fermented drink made with infusions of dry brown bread). Urban dwellers should avoid being out in the sun too long, particularly with their heads uncovered. Health-promoting measures are enacted at work-enterprises: hard physical work and the carrying of heavy loads in the heat of the sun require special training, light clothing, and a proper drinking cycle.

## **Treatment**

Urgent treatment is essential for good results. The first thing to be done is to relieve the patient of anything he may be carrying, place him in the shade, unfasten and remove his clothing. Ice is applied to the patient's head, neck and spine, cold water is poured over his face, and his chest is slapped with a cold wet towel. For cardiac weakness injections of caffeine, camphor, cardiazol and strophanthin (0.5 ml of an 0.05 per cent solution intramuscularly) are prescribed, oxygen mixed with carbon dioxide is given for inhalation, glucose is injected intravenously, and small volumes of physiologic salt solution (200-400 ml) are injected subcutaneously; lobelin is given for respiratory difficulty.

In cases of high arterial pressure intracranial pressure is decreased by bloodletting or lumbar puncture.

### **EFFECT OF HEAT ON FLUID-ELECTROLYTE METABOLISM**

The effect of heat on the human body is manifested by changes in a number of physiological functions.

Fluid-electrolyte metabolism is the first to be affected. As has already been mentioned, perspiration is the principal mechanism of thermoregulation; a small part of fluid (10-15 per cent) is evacuated through the bladder and the lungs. According to English and German authors who studied fluid metabolism in the tropics and the Middle East the maximum amount of sweat secreted diurnally by a human being is 12 litres.

Investigations carried out in Tashkent and Khorezm in July (I. A. Kassirsky and Y. V. Poslavsky, 1931) showed that manual labourers lose as much as 4-5 litres of fluid and 20-30 g of sodium chloride with sweat whilst working in the very heat of the sun.

The present authors, in association with G. I. Samokhin evolved a method for titrating chlorides after total ablution of the body in special camp baths. V. K. Solovyov (1933) registered up to 3 kg in weight losses per day due to perspiration among soldiers on the march in the summer. G. I. Samokhin (1936) worked in Central Asia in the month of July; he established that the loss of sodium chloride among soldiers on the march was very high—up to 20 g diurnally. In Tashkent and amidst the sands of Khorezm the volume of water drunk up by a manual labourer during the hot summer months may be as much as 5-6 litres, while the volume of urine voided decreases to 300-500 ml, micturition occurring no more than 1-2 times a day (4-5 micturitions are the usual winter figures).

The human body does not remain indifferent to such excessive respiration. Anybody who has lived or lives in warm lands knows that a long walk in the streets of a city in July, particularly whilst carrying some small package, bag, or bundle, usually resolves into a march from one cold drink booth to another. People have a craving for enormous intakes of water, and the more they drink the more they perspire, while the intolerable thirst remains and forces them to drink still more and more. In a physi-

ological sense thirst belongs to a category of general sensations objectively displayed by a positive motor response to water. Subjective sensations are dryness in the mouth and throat, general weakness; in the presence of considerable fluid deficits sugar does not melt in the mouth, nor does it evoke any sensation of taste; dry food cannot be swallowed, the voice becomes hoarse; the volume of circulating blood decreases, the blood becomes more viscid, systolic volume decreases, while the frequency of the heart-beats increases.

Thirst is a condition during which a peculiar "water hunger" develops: this deficit is the beginning and end of a cycle frequently observed in pathologic conditions, called *circulus vitiosus*. In its extreme status this condition is called the *drinking disease*, which not infrequently affects workers in hot workshops and is manifested by disturbances in a number of organs and systems.

It must be taken into account that normally the fluid balance is established inertly; after heavy water losses the normal equilibrium is established no sooner than in 24 hours. Restoration of the electrolyte balance is still slower (N. V. Danilov). When the environmental temperature is high and there is a water deficiency in the body the latter intensively uses up its carbohydrates and fats, its proteins break up, acidosis develops. Symptoms of the drinking disease are acute thirst, poor appetite or complete anorexia, general malaise, weakness, dyspeptic trouble (eructation, sometimes fetid), tremors, loose stool. Gastric disturbances are due to distention of the stomach caused by drinking great quantities of water, followed by gastritis, while diarrhea is due to the loosening effect of the great volume of liquid taken and, particularly, of the salts introduced with this liquid. The authors have observed in the summer months many patients complaining of foul eructation, loss of appetite, loose stool, malaise and weakness who associated their condition with excessive fluid intake. More or less expressed forms of the drinking disease are observed in non-acclimatised servicemen during prolonged marches over desert-land in the summer heat. After the body rapidly loses over 10-15 per cent of its weight the patient's condition becomes threatening: his eyes are sunken, vision and hearing deteriorate sharply, esophageal spasms and strangury are observed. The excessive volume of water introduced into the body does not help the patient, it not infrequently even aggravates his condition, leading to disturbances of the neuromuscular system, impairment of motor co-ordination, and the appearance of nausea, tremor, convulsions, etc. The above symptoms appear more rapidly when the drinking water has a low electrolyte content (for this reason mountain climbers avoid drinking water thawed out from glaciers) (N. V. Danilov).

### **Prophylaxis and treatment**

In hot climates the inhabitants, particularly newcomers, should be informed of the importance of regulating their fluid intake throughout the hot season.

The diurnal volume of water is established by environmental conditions, intensity of muscular work, nature of metabolic processes governed by the nervous system, quantity and quality of food ingested. Fluid losses are an essential factor. A. I. Venchikov (Ashkhabad, 1952) attaches great importance to the function of the sudoriferous apparatus. This author recommends "creating such conditions for the activity of this apparatus that it should secrete sweat uniformly, thus providing continuous evaporation, and, consequently, cooling of the body".

The "drinking norm" is, according to N. V. Danilov, the minimum volume of water taken in drink that maintains the diurnal fluid-electrolyte balance at a normal level. In hot atmospheres one should strive not to take in any excessive amount of water—"in other words, as the matter stands, rather than teaching people to tolerate water deficits we should teach them not to drink water to excess" (N. V. Danilov). For instance, in the hot belt of Central Asia, where the atmospheric temperature reaches 39-40° C, manual workers occupied in the open air should drink up to 3 litres of water during their work hours, the round-the-clock norm being 6 litres (O. P. Molchanova, M. Y. Marshak, Y. F. Rozanova, et al.). At lower temperatures the daily requirements in drinking water are lower—3-4 litres.

N. V. Danilov investigated two groups of workers in the vicinity of Tashkent: one group drank spring-water freely, while the other group observed a special drinking cycle. As a result a typical form of the drinking disease developed among the inadapted workers in the first group, while no such incidences were noted among the second group. N. V. Danilov urges the necessity of observing a combined fluid and solids cycle during the summer heat. The compilation of rational food and water dietaries are based on the scientific principles of Ivan Pavlov's teachings on digestion. Fluid ingested with food is retained in the body for a longer time. Food must be taken at definite hours, in accordance with the conditioned time reflexes that have been formed.

Dehydration impairs the appetite, therefore 250 ml of tea taken before a meal is beneficial. The volume of the food and its consistence should be such as to create optimal conditions for the mechanical stimulation of the gastric glands; as much tea as is wanted may be taken after meals, until thirst is completely slacked (N. V. Danilov). O. P. Molchanova studied the energy expenditures of field workers; she recommends that this category receive 4,000 calories in the daily three meals, and that the food be brought directly to their site of work. The protein content should not exceed 120 g, as greater volumes of protein intensify heat generation and renal activity.

It is a national custom with Uzbeks, Turkmens, and Kazakhs to round off every meal with green tea. For excessive fluid losses with perspiration (over 4 litres) it is recommended to take an additional 5 g of salt with food (in Turkmenia, where the drinking water is rich in salt, this is not necessary). The need of taking increased amounts of vitamins in the hot time of the year is common knowledge; vitamins break up intensively in

high environmental temperatures. Below we cite several illustrations of fluid management for hot climates, in accordance with the proposals set forth by a number of authors.

A. I. Venchikov recommends the following drinking cycle for the climate of Turkmenia: tea or water to complete satiation of thirst in the morning, after breakfast; during the next two hours no water is taken. Sensations of thirst or dryness in the mouth are alleviated by rinsing the mouth and throat with small portions of water. If the feeling of thirst is suppressed during the first hours it is tolerated with greater ease later.

During the third and fourth hours a glass of water is drunk in small gulps. At the interval for the mid-day meal a second glass is taken before eating, and before commencing work again thirst is slacked completely. The same routine should be observed in drinking water during the second part of the day.

S. Maximenko (1948) proposed the following routine for water intake on a 25-30-km march.

1. The men drink tea or water to their fill (600 ml) after breakfast on the morning of the march. The individual water flasks are filled with good drinking water or cold tea.

2. On the march and during the first two short halts no drinking is permitted—it is recommended to simply rinse the mouth with several mouthfuls of water, but it is better not to do even this, as a thirsty person, once he has a water-bottle at his lips, will not be able to resist the temptation to drink.

3. During the third and fourth halts it is permissible, after a rest of 5-6 minutes (and only if the thirst is very great) to drink 250 ml of water very slowly, trying to keep it in the mouth as long as possible.

4. No immediate drinking should be done when the halt for the long rest is called; first the mouth and throat are rinsed for some time, and then no more than 150 ml of water is drunk. Before marching it is recommended to quench the thirst completely. The flasks are rinsed out and filled with fresh water.

5. No water should be taken during the short halt after the mid-day meal. At the second and third short stops the men are advised to drink no more than 250 ml of water after a short rest if they are thirsty.

6. When encamping for the night, as well as during night halts, the men should not drink immediately the halt is called; as much water as is wanted is permissible after supper.

A prominent specialist on fluid-electrolyte management E. Adolph does not attach any importance to the nature of the liquid with which thirst is quenched; however, Soviet physiologists who have studied the problem in practice disagree with this opinion.

Training, will-power, and self-restraint are indeed important factors in controlling the drinking disease, but an additional factor that must be taken into account is the thirst-slacking property of the constituents ingested with water.

The first thing the majority of authors dwell upon is the introduction of sodium chloride; this is done to compensate the depletion of chloride, on the one hand, and to fixate the water in the blood and tissues, on the other. This method has been accepted in high-temperature workshops: the workers drink water containing 0.5 per cent of table salt (the total amount of salt thus ingested may be 10 g).

Green tea is widely used as a thirst-slacking fluid by the peoples of Central Asia. V. K. Solovyov (1933) and A. S. Sadykov (1939) made a close study of the value of green tea in this respect. Cold acidified tea quenches the thirst very efficiently (F. G. Krotkov). N. V. Danilov cites a number of various thirst-quenching liquids. Thus, carbonated water is highly popular (A. I. Volkovich). The Turkmens and Uzbeks use a certain cheese — “gourd” (dried salted fermented curds)—for overcoming thirst. Travellers in the desert add a little condensed milk to their drinking water. In Russia a fermented infusion of brown bread (kvass) is a most popular drink for slacking thirst. Some authors list salted tomato juice and compote (dried-fruit infusions) among thirst-quenching agents.

There is as yet no consensus of opinion in regard to the role of sugar in lowering the fluid balance and improving the general status.

It is, indeed, known that workers exposed to high temperatures in sugar refineries do drink large quantities of sweet water and consider that this heightens their tolerance of environmental heat. A. N. Kabanov (1934) made some objective observations of such employees and found that the introduction of sugar did not lower the body temperature of overheated individuals, although it did have a favourable effect on their pulse and respiration. The best effects were obtained when the subject drank 1-1.5 litres of water with 10 g of table salt and 10 g of sugar. F. G. Krotkov recommends acidified tea, kvass, and some other drinks for quenching thirst during heat.

Perhaps the positive role of sugar is more forceful at times of intensified muscular work in high environmental temperatures, as glucose inhibits decomposition of proteins in the body and regulates the function of one of our most important internal organs—the liver\*.

When people take enough fruit in their food during the hot season, including thirst-quenching fruits, they find that this promotes a cheerful disposition and their general feeling of well-being, and thus teach themselves to use these foods for controlling heightened fluid balances. Moreover, the value of fruit and melons is enhanced by their diuretic action, as they decrease the volume of liquid that is evacuated through the sweat glands, thereby somewhat decreasing the lability of the latter and thus being conducive to a lower rate of fluid metabolism.

The natural juices of grapefruits, oranges, and lemons—widespread drinks in America—are also good thirst-quenching agents.

---

\* A number of experimental investigations carried out in Tashkent by Rachkov showed the introduction of glucose to decrease energy losses of oxygen, and had a beneficial effect on the circulatory system and general disposition of subjects examined in hyperpyrexia conditions.

A famous chemist of the 18th century, John Priestley, was the first to propose charging water with gas, a method now widely employed in the preparation of cooling beverages. The procedure lends a certain taste to the drink; if a salty beverage has to be taken it is best given carbonised: the pleasant taste of carbonic acid disguises the salty taste of the drink.

Certain authors, basing themselves on empiric observations, hold that aerated water quenches thirst better than plain water—hence the popularity of gas-charged water in the summer.

Cold beverages slack the thirst better than warm ones do. Undoubtedly, taste plays an important part in quenching thirst; an aerated beverage that “burns” the oral mucosa makes it less sensitive for some time, owing to which a feeling of quenched thirst is retained. In so far as the ingestion of excessive quantities of water promotes thirst anyhow such local thirst-slacking agents are also acceptable, all the more so as in the arid desert water may have to be economised on.

Our attempts at decreasing the water balance by lowering the body temperature with pyramidon was not successful. A better effect was obtained in the drinking disease by half a tablet of theophedrin (a compound resembling theominal, as it contains theophylline, theobromine, caffeine, pyramidon, phenacetin, ephedrine hydrochloride, luminal, pulverised belladonna leaves, and lobelin hydrochloride or cytisine).

Thirst is rapidly quenched and the fluid balance swiftly decreased by means of *frequent cool sponge-baths* or *bathing*. This route for regulating the fluid and heat balance of the system must always be remembered in cities, villages and river valleys.

### EFFECT OF HEAT ON THE DIGESTIVE FUNCTION

Aside from disturbances of the fluid-electrolyte balance a very important factor in man's behaviour in tropical and subtropical lands is, naturally, the digestive function. The sharp deterioration of appetite, particularly for meat and fats, is well known, as is the unwillingness to eat during the hottest time of the day, the bitterness and dryness in the mouth, the weight on the stomach. Physiological observations carried out by I. P. Razenkov (1934) in special thermal chambers showed a decrease in gastric secretion. According to the data of N. V. Danilov obtained in the hot season in Tashkent inhibition of salivary secretion is concurrent with a decreased gastric response (secretion) to standard food reflex stimulants; gastric secretion in dogs is lowered by 12 per cent in the heat of the sun. Current data presented by Turkmenian authors who employed the Bykov-Kurtsin method show that heat causes a diminution of gastric secretion (V. Yusin, F. Sultanov, B. Mamedov, et al., 1958). However, N. Kuznetsov (1951), in his capital study of the problem in Turkmenia (June-August) established that the decreased acidity of the gastric juice is not the leading physiologic mechanism of these disturbances. The loss of appetite is probably connected with severe depression of the autonomic nervous system, as well as with the drinking disease (leading to diminution



of secretion of digestive juices). Additional factors are exhaustion, malaise, depression, and decreased capacity for mental work in persons inadapted to hot climates. According to personal data basic metabolism decreases 10 per cent in hot environments.

N. I. Latyshev is of the opinion that the depletion of the system of potassium ions is very important in the development of the symptomatology of the condition of the digestive tract (in his opinion the nervous system is particularly susceptible to potassium deficits). For this reason, he holds, people in tropics have an urge for a vegetable diet in the summer — vegetables and fruits have an abundant potassium salt content.

The change occurring in intestinal digestion during hot periods deserves particular attention. Here the most prominent part is played by the fermentative processes that are so important in the etiopathogenesis of intestinal ailments in warm lands.

When the diet is properly balanced and no carbohydrate monophagism is present (i. e., the diet includes various proteins, fats, and carbohydrates) no trouble is experienced.

The greater frequency in warm countries of acute and chronic colitis as compared with temperate zones is associated with the chemical irritation of the small intestine by the acid contents, and the mechanical irritation of the large intestine by coarse roughage, the latter injuring the intestine, causing inflammation of its mucosa; under such conditions the permeation into the intestines of endo- and exogenous infections takes place sooner and more frequently.

Children's summer diarrheas in warm lands deserve specific notice, as they are definitely connected with overheating. R. S. Gershenovich (1928) in his book *Introduction to Pediatrics* pointed out that the so-called toxic dyspepsia of children living in hot climates (this includes simple dyspepsia and catarrhal enteritis) is extremely prominent in May, and subsequently, as the heat intensifies, the morbidity reaches its peak in July, after which it decreases, so that by September-October only solitary cases are noted, and almost none at all in the winter. The importance of overheating in so-called toxic dyspepsia is confirmed by the fact that in June and July in Uzbekistan the number of such disorders is particularly high as compared with other types of diarrhea, attaining a menacing figure of 20 per cent, while their corresponding incidence in Moscow in the same months is no higher than 4 per cent. Favourable climatic conditions mitigate the gravity of the course of toxic dyspepsia.

Not only toxic dyspepsia, this gravest form of intestinal disturbance in children, but also any diarrhea in general is associated with meteorological factors. Statistics of all countries show diarrhea to be present among children throughout the year; however, its incidence is rather constant in the autumn and winter months, while a sharp increase occurs in the hottest months (May, June, July, August).\*

---

\* Naturally, some responsibility for this "jump" should be attributed to dysentery, but still the most important factor is summer dyspepsia (particularly in nursing infants).



by the Uzbek Mother and Child Welfare Institute published some illustrative data on the diarrhea incidence among children over one year of age in Tashkent (Table 12, in percentages of the total number of child patients received at the infant health centre. After R. S. Gershenovich).

Children's Diarrhea in Tashkent		
Year	Minimum	Maximum
	Percentage of diarrhea cases among all patients	Percentage of diarrhea cases among all patients
1925	March 6.21	June 50.81
1926	February 10.58	June 58.68
1927	December 9	July 49
1928	February 5.09	July 45
1929	January 1	July 24
1930	February 1	July 20

The connection between summer diarrhea in children and the effect of heat was established a long time ago, and such authoritative pediatricists as N. Filatov, Finkelstein, and others held the pathogenesis of these diarrheas to be associated with the hyperpyrexia occurring in children owing to the imperfect function of their thermoregulating mechanism.

Some of the following symptoms are manifested when the child's system is overheated:

1. Immunity decreases.
2. The bactericidal action of the digestive juices decreases (thus the possibility of endogenous infections is enhanced).
3. Tolerance toward various foods decreases (hence the harm of over-feeding children and of improper nutrition in general).

### Prophylaxis and treatment

Nutrition in the tropics (during the hot season) should be just as diversified as in any other climate. Carbohydrate monophagism is antithetic to the principles of physiology of nutrition, and it leads to fermentative dyspepsia, protein deficiencies, and polyavitaminosis.

It is advisable to decrease the norm of proteins and fats by 15-20 per cent. Practice has shown that the best meal-schedule for the summer is the following: a heavy breakfast in the morning, on the hottest days a light lunch or snack in the middle of the day, and a full dinner in the evening (at 6-7 o'clock), when the heat subsides.

Fermentative dyspepsia is combated by a restriction of coarse cellulose (roughage), and course sorts of bread. The local population fares best on the food century-old habit has accustomed it to.

## EFFECT OF HEAT ON THE CARDIOVASCULAR SYSTEM

During the summer heat weakness and decreased work-capacity develop, and therefore there has been much talk of the negative effect of heat on the heart. However, this is a false conception.

The reactivity of the autonomic nervous system and the degree of circulatory asthenia associated with it are held to be due to the fact that the negative effect of heat is first manifested on the heart. Now everyday facts speak of the opposite. It is common knowledge that in warm zones people with normal nutrition and work live longer (in the Soviet Union Abkhazia and Georgia are good examples). It is evidently in connection with climatic conditions, as well as with nutrition, that the incidence of coronary thrombosis is much lower in the south of Spain, on Ceylon, and in British Guinea than in northern lands (Z. I. Umidova). Z. I. Umidova (1946) and A. K. Khojayevev (1953) studied hemodynamics in Tashkent and in the northern climatic zone; they concluded that in the first instance the displacements noted are rather positive than negative. Arterial pressure, pulse, and respiration do not normally overstep the boundaries of physiological oscillation, while it is not uncommon for arterial pressure to return to normal in hypertensive individuals (Z. I. Umanova, A. K. Khojayevev). Simultaneously some increase of vascular and tissue permeability is noted, and also a reduction of adrenal function (adynamia) (V. Yusin et al.).

A most circumstantial study of healthy subjects in hot climates was made by M. I. Slonim (1949). This author investigated changes in pulse rate and in arterial and venous pressure in the summer heat; for comparison he took the same measurements in the winter months. He established only a tendency to a decrease of venous pressure and some acceleration of the pulse as factors of acclimatisation. As regards the minute volume—the essential point of hemodynamics—this reaction is of two kinds: in one group of individuals the minute volume increases to meet the requirements thermoregulation sets the cardiovascular system; in young, healthy servicemen this increase is attained by the most profitable route in the energetic sense—at the expense of enlargement of the systolic volume without any noticeable acceleration of the pulse; in the other group of subjects investigated the winter minute volume is retained in the summer without any noticeable increase of the pulse rate—thermoregulation is evidently effected by the redistribution of the blood.

The conclusions reached by M. Slonim show that no diminution of the functional capacities of the cardiovascular system takes place during intensive summer heat. This was confirmed by ECG studies.

The present authors agree with the general conclusions of Slonim: insignificant hemodynamic displacements that occur in warm climates during the hottest season are adaptational features (acclimatisation) rather than otherwise, and adaptational changes per se in hemodynamics are of no specific pathologic value.

Oxygen circulation in subjects affected by cardiovascular failure was studied by A. K. Khojayevev in Tashkent during the summer; the results were compared with data obtained in the temperate zone of the U.S.S.R. Khojayevev investigated the oxygen capacity of the blood, its volume in the arterial blood, the arterial-venous difference, the percentage of oxygen utilised by the tissues, the oxygen content and saturation of the venous blood, and also carbon dioxide blood values. One hundred patients with valvular deficiencies and various degrees of heart failure were investigated. The gas indices of the blood were also studied on healthy subjects.

A. Khojayevev was able to prove that the status of the oxygenation of the system of healthy subjects did not deviate from normal during the summer heat (when the thermometer showed 42°C in the shade). Measurements of the pulse rate, arterial pressure, respiration and body temperature of healthy people confirmed the fact that deviations in these indices do not exceed normal physiological oscillations during the highest environmental heat. A decrease in the minimum pressure is due to acceleration of the blood flow, dilation of the capillaries and of superficial peripheral veins — all favourable hemodynamic signs.

Comparative studies of the gaseous components of the blood in the summer and winter months in cardiac patients showed no negative effect of the summer heat on oxygenation of the system. The same is true of a comparison of data on patients with heart trouble living in Tashkent and in Moscow. Khojayevev notes a similar state in regard to a number of biochemical indices — glutathione, lactic acid, etc.

Circumstantial investigations led Khojayevev to the only correct and objective conclusion: "Our data do not reveal any harmful effect of the climate of Tashkent on systemic oxygenation neither of healthy subjects adapted to that climate, nor of subjects with cardiovascular failure." The personal practical experience of the present authors in Central Asia permits them to affirm that the course of cardiac diseases in the hot regions of Central Asia is no different from what is observed in the temperate zone of the U.S.S.R., while the high mean longevity among the local population confirms our opinion of the absence of any harmful effect of heat on the cardiovascular system. Moreover, the rate of rheumatic diseases in the hot and arid regions of the republics of Central Asia is lower than in the north, particularly as compared with the Baltic republics.

We see no particular obstacles in the way of sending valvular failure subjects or recent rheumatism convalescents to the south for a prolonged time or during the hot season. The above-mentioned beneficial factors of climatotherapy should be widely utilised for curing the residual symptoms of rheumatism and for the prevention of new attacks. They should be resorted to freely, with no fear of their alleged "harmful" effect on the heart.

#### EFFECT OF HEAT ON THE SKIN

Besides certain specific skin conditions associated with insolation (for instance, hydroa vacciniforme) and the parasitic fungal fauna so widespread in hot lands (fungous skin diseases) various intertriginous erythemas are frequently observed during the hot season; in particular does intertrigo affect people participating in long, protracted marches. This should be considered when working out designs of hygienic clothing and footwear. The subsequent contamination of intertriginous surfaces is frequently the cause of furunculosis, folliculitis, axillary and pararectal abscesses; such trouble may be avoided by frequent ablutions, personal cleanliness, etc.

Other skin conditions observed are sunlight erythema (actinic dermatosis), cracked lips, and some other pathological reactions.

## PERSONAL HYGIENE AND DAILY ROUTINE

It is advisable to get up early in the summer; the early sunrise and bright light call one to be up and about anyhow. Six or seven o'clock is the time to rise, take a walk in the fresh air and do exercises for 15-20 minutes, and then have breakfast.

Work usually begins at eight o'clock, to coincide with the coolest hours. In many warm lands some enterprises have an intermission from noon to evening; work is recommenced at 6 p. m. and continued until nightfall. The long intermission is utilised for various purposes—lunch, sleep, reading, bathing.

It is recommended to take a bath or shower after work, before leaving for home. If the enterprise does not provide its employees with facilities for ablutions such facilities should be installed at home.

A few words about outdoor bathing. It is recommended to stay in the water for no longer than 10-15 minutes, moving around all the time; the best time for sunbaths is between 10 and 12 o'clock in the morning, when the rays of the sun are not too intensive, but 5 p. m. is also not a bad time. However, moderation must always be observed in sunning, beginning with 5 minutes and gradually going up to 30 minutes, but no longer. Physiotherapists advise test sunbaths (so-called *insolatio intermittens*), alternating insolation with rest in the shade. This provides for maximum utilisation of solar energy, while the body is protected against hyperpyrexia. Of late physicians have been replacing the minute computations for insolation by caloric values, as the latter is more precise in a physical sense; the calorific values contain corrections of a biological nature for each given case of weight and height, and for the individual features of the exposed subject.

During sunbaths the head should be lifted and protected from direct sunlight with a parasol or tent, a white kerchief, or towel. It is undeniably harmful to lie in the sun for hours on a time, as children and inexperienced adults do; the harmful effects of insolation have been dwelt on above. Sunbaths are not permissible after bathing, as wet skin is easily burnt. Air baths in the shade (aerotherapy) are very salubrious. Such baths may be taken intermittently over one to two-and-a-half hours in the shade on a wind-protected bank. After bathing the body should be thoroughly dried (otherwise the remaining moisture will rapidly conduct heat), then one should rest for about ten minutes in the shade and set off for home in light, loose clothing.

Some people like to take a shower in the evening before going to bed. This is not a bad idea, as the water removes perspiration and dust and soothes the nervous system. In the U.S.S.R. the evenings belong entirely to the working people, and are spent in parks, recreations grounds, etc. Cool and well-designed areas for relaxation and recreation in the evening provide an excellent rest. Seven to eight hours of sleep in the summer, including a nap in the daytime, is enough for adults.

Particular attention should be paid in the summer to cleanliness of clothing; the latter should be washed more frequently to enhance its thermoregulating properties. Clean clothing and frequent bathing protect the skin from dirt. Hygiene of the feet is a salient point in warm climates.

The eyes are frequently not attended to sufficiently in warm lands. These organs are easily irritated and tired out by very bright light, particularly when the sun is in the eyes for protracted periods of time (as is the case with motor-car and street-car drivers), or when a person reads in the sun and generally spends much time in its heat. The authors have observed incidences of eye diseases connected with insolation.

Dark glasses (smoke-coloured) are recommended for protecting the eyes against heat and chemical rays. Some specialists recommend blue glasses, but they let the ultraviolet rays through.

Sport has a high hygienic value in the tropics; the importance of morning exercises has already been pointed out. The balance of sport activities should be left for the evening. Sports include ordinary physical exercises, but gymnastics combined with recreation are preferable: football, basketball, tennis, volley-ball. Sport is highly salubrious in the summer as it trains the muscles, leading to a lower expenditure of phosphocreatine and to a reduction of lactic acid accumulation in the blood and tissues; the production of lactic acid is greatly increased during physical work or exertions in the heat of the sun.

In southern lands it is very important to ensure normal sleep by protecting people against the assaults of various bloodsucking insects (fleas, mosquitoes, bedbugs); protection is attained by maintaining cleanliness in living quarters and by the installation of screens, bed-nets, etc. The abundance in warm lands of rodents, roaches, and flies and the harm they engender should mobilise efforts for ridding homes of them and exterminating them in general.

Labour hygiene in the summer deserves a place to itself. Only some general points are indicated here.

1. Work efficiency and the health of workers occupied under conditions of excessive heat should be guaranteed by a maximum of labour mechanisation facilities (as in high-temperature enterprises).

2. It is advisable to have several 10-15 minute recesses with rest in shady places during work; experiments carried out by a number of authoritative researchers showed positive results with such intermissions. The details of the work and rest cycles as applied to concrete conditions of work, temperature, and locality should be evolved by special labour committees.

3. All requirements regarding clothing, nutrition and fluid intake, dwelt on above, concerning people occupied in various fields of work, should be observed with particular strictness.

4. Particular attention should be directed to special housing construction in warm zones.

## INDEX

- Abreviata caucasica, 341
- Acanthocheilonema perstans, 316
- Acclimatisation, 443
- Acetarstone (see osarsol)
- Acrichin (see quinacrine, mepacrine), 23, 91
  - contraindications, 94
  - dosage
    - in malaria, 101
    - in malarial pernicious anemia, 104
    - pediatric, 106
    - prophylactic, 107
  - psychoses due to, 93
  - side effects of, 92
  - therapeutic properties of, 92
- Actamer (see bithionol)
- ACTH, 310, 317
- Actinomyces, 404
- Adaptation, heat, 443
  - impairment, 443
- Adolocercaria, 271, 277
- Adrenalin, 328, 388
- Aedes aegypti, 373–375, 377, 378, 380, 382, 384, 388, 389
- Alcopar, 300, 302
- Amaryl mask, 384
- Amebiasis, 203–219, 427
  - clinical classification, 212
- Ameboma, 214, 216
- Aminarson, 218
- Aminophylline (euphylline), 440
- Amodiaquin, 91
  - dosage in malaria, 100
  - prophylactic, 107
- Amphoterrycin, 407, 409, 410
- Amphymerosis, 255
- Amphymerosus noverca, 255
- Anasarca, 278
- Ancylostoma, 293, 294
- Ancylostomiasis, 18, 293
- Ancylostomidoses, 293–302
- Anemia, in malaria, 42, 71
  - metamalarial, hypogenerative, 58
- Anguillula stercoralis, 319
- Anguilluliasis (strongyloidiasis), 319
- Anopheles, 23, 24, 26, 33, 34, 305
  - gonadotrophic cycle, 35
  - oviposition, 25
  - susceptibility to infestation, 27
- Anthiomaline, 236
- Antianemin, 238, 299
- Antimonous preparations, 241, 251
  - contraindications, 237
- Antimony lithium thiomalate, 236
  - potassium tartrate, 241
  - sodium tartrate, 235
  - trivalent, 235
- Antisnakebite serum, 419
- Antrypol, 150, 313
- Arsobal, 151
- Ascariasis, 17
- Ascorbic acid, 238
- Assassin bug, 153
- Atabrine dihydrochloride, 23, 91
- Ataxic syndrome, 432
- Atebrin, 23
- Athiaminosis, 430
- Aureomycin (biomycin), 199, 201, 398, 399
- Avitaminoses, 20
- Baermann method, 322
- Balantidiasis, 427
- Banocide (see hetrazan)
- Barbiers, 430
- Bartonella, 400, 402
- Bartonellosis, 400–403
- Bayer 205 (see antrypol)
- Bayer 7602, 158
- Bayer 9736, 158
- Beetles, poisonous, 416
- Bejel, 202
- Benzene hexachloride, 371, 372
- Beriberi, 430–436
  - chronic forms of, 432

- Bertielliasis, 291  
 Betanaphthol, 279  
 Bicillin, 198  
 Bigumal (paludrine), 23, 91  
     dosage, in malaria, 101  
     in malarial pernicious anemia, 104  
     prophylactic, 107  
     therapeutic properties of, 94  
 Bile drainage, 252  
 Bilharziasis, 226  
     intestinal, 231  
     mansoni, 231  
     schistosomiasis, 231  
     treatment of, 235  
 Biomycin (aureomycin), 183, 218, 224,  
     310, 347, 350, 354, 359, 363, 382, 395  
 Biskra button, 130  
 Bismuth, 201, 202, 224  
     subgallate (dermatol), 216  
     subnitrate, 216  
 Bites, of  
     beetles, 416  
     karakurt spider, 411  
     scorpions, 415  
     snakes, 417  
 Bithionol, bitin, 268  
 Black sickness, 110  
 Black Widow spider, 411  
 Blanfordia nosophora, 256  
 Blood, in  
     chronic ulcerative colitis, 222  
     spirochetel jaundice, 181  
     tick-borne relapsing fever, 170  
 Blue vitriol, 242  
 Bodies, immune, 47  
 Borovsky bodies, 131  
 Borrelia, 160  
 Bubo, climatic, 393  
  
 Cachexia  
     aphthous, 420  
     hypophyseal, 420  
 Caffeine, 447  
 Calabar swellings, 314–316  
 Calcium,  
     arsenate, 242  
     carbonicum, 428  
     chloride, 428  
     gluconate, 414  
     hypochlorite, 371  
     preparations, 328  
 Camoquin (amodiaquin), 91  
 Camphor, 415, 447  
 Campolon, 238, 299  
 Canine typhus, 187  
 Capillaria hepatica, 332  
 Carbarsone (aminarson), 217, 218  
 Carbon tetrachloride, 275, 300  
 Cardiazol, 447  
  
 Caricide (see hetrazan)  
 Cercariae, 226, 227, 242, 243, 244, 257,  
     261  
     caudate, 247  
     of fasciola fluke, 270  
     of Fasciolopsis fluke, 277  
     of paragonimiasis, 265  
 Cercarial dermatitis, 242  
 Ceylon sore mouth, 420  
 Chagoma, 155  
 Chancre, lymphogranulomatous, 394  
     trypanosome, 148  
 Chenopodium oil, 262, 282, 300, 301, 335,  
     341  
 Chlamydospores, 405  
 Chlamydozoaceae, 393  
 Chloramphenicol (chloromycetin), 199,  
     398, 399  
 Chloridin (pyrimethamine), 91  
     contraindications, 96  
     dosage in malaria, 102  
     prophylactic, 107  
     therapeutic properties of, 96  
 Chloromycetin, 350, 359, 402  
 Chloropicrin, 371  
 Chloroquine, 91, 251, 268  
     diphosphate, 217  
     dosage  
         in malaria, 100, 101  
         in pernicious malaria, 105  
         prophylactic, 107  
     phosphate, 254  
     sulfate (nivachin B), 105  
 Chlorosis, Egyptian, 293  
 Chrysops, 314  
 Cinchona bark, 22  
 Cinchonine, 22  
 Cirrhosis of the liver,  
     postmalarial, 78  
 Climate, effect on human body,  
     442–458  
 Climatotherapy, 456  
 Clonorchiasis, 246–252  
 Clonorchis sinensis, 246, 249  
 Cocaine hydrochloride, 388  
 Coccidioidal granuloma, 408  
 Coccidioides immitis, 408  
 Colitis  
     fermentative, chronic, 220, 221  
     ulcerative, chronic, 220–225  
 Colostomy, 224  
 Complement fixation, 363, 381  
 Cordiamin, 415  
 Cortin, 429  
 Cortisone, 310, 429  
 Councilman bodies, 387  
 Coxiella conori, 351  
 Cryptomerozoites, 24  
 Cryptozoites, 24

Cutaneous leishmaniasis (see Leishmaniasis)  
 Cyclops, 325, 326  
 Cysts, quadrinucleate, 204, 209  
  
 Darachlor, 102, 107  
 DDT, 152, 158, 172, 371, 372, 378, 388, 389  
 Dengue, 377–378  
 Dissipation, heat, 443  
 Dermacentroxenus, 348, 354–356  
 Dermatitis, cercarial, 242  
 Dermatol, 216  
 Dermatoses, simulated by  
     cutaneous leishmaniasis, 136  
 Diarrhea alba, 420  
 Diarrheas, summer, of children, 453  
 Diathermocoagulation, 142  
 Dibutyl phthalate ointment, 242  
 Dimedrol, 237, 245, 316, 317, 328  
 Dimethyl phthalate, 242, 372  
 Dioctophyma renale, 343  
 Dioctophymosis, 343  
 Dipetalonema perstans, 316  
 Diphyllbothrium, 288  
 Dirofilaria, 317, 318  
 Disease  
     blue, 347  
     Chagas's, 152  
     Corrion's, 400  
     Darling's, 409  
     Date, 373  
     drinking, 448  
     Durand-Nicolas-Favre, 393  
     fourth, venereal, 393  
     Haneman-Schenker, 409  
     Hayem-Widal-Abrami, 78  
     heliotrope, 437–441  
     Katayama, 226, 238  
     leptospiral, 174–190  
     Luz-Splendore-Almeida, 406  
     natural-endemic, 17  
     Parrot, 390  
     Posadas', 407  
     Quinke's, 316  
     Simmond's, 424  
     Stuttgart, 187  
     tsutsugamushi, 357  
     vitamin deficiency, 20  
     Weil-Vasiliev, 175  
 Dithiazanine, 323  
 Ditrazin, 309, 339  
 Donovan bodies, 396, 397, 399  
 Donovanian granulomata, 386  
 Donovanosis, 396  
 Dracontiasis (dracunculosis)  
 Dracunculosis, 324–330  
     clinical aspects, 328

    pathogens of, 324  
     treatment of, 328  
     vectors, 325  
 Dracunculus, 324, 325, 330  
 Dysentery  
     amebic, 203  
     bacillary, 427  
     bilharzial, 231  
     schistosomal, 231  
  
 Echinocasmiasis, 282  
 Echinocasmus oerfoliatus, 282  
 Echinostoma, 280  
 Echinostomiasis, 280  
 Edema, malarial, 75  
     hemoglobinuria, 60–64  
 Ehrlichia lymphogranulomatis  
     Moshkovski, 393  
 Ehrlichia psittaci, 390  
 Elephantiasis, 307, 312, 394  
 Emetine, 216  
     hydrochloride, 274  
 Enteritis,  
     fermentative chronic, 428  
     treatment of, 428  
     of warm lands, 426  
 Entamoeba histolytica, 203, 205–210  
 Ephedrine, 328  
 Eruption, creeping, 340  
 Eschar, 357  
 Esophagostomiasis, 336  
 Espundia, 142, 143  
 Esthiomena, 393  
 Euparyphiasis, 281  
 Euparyphium, 381  
 Euphylline, 440  
 Euquinine, dosages, 102, 106  
 Eurythrema pancreaticum, 287  
 Eurythremiasis, 287  
 Evolution of infections, 20  
 Exanthema, infective, epidemic, 351  
 Exoerythrocytic stages of plasmodia, 24  
  
 Fasciola hepatica, 269, 276  
     giganta, 269  
 Fascioliasis, 269–275  
     ectopic, 270, 272  
     pharyngeal, 272  
 Fasciolopsiasis, 276–279  
 Febrigenes papatasii, 366  
 Fern extract, 249, 259, 262, 263  
 Ferrum carbonicum, 299  
     reductum, 299  
 Fever  
     Amaryl, 379  
     Barbiero, 152  
     blackwater, 60



- breakbone, 372  
 canebrake yellow, 60, 187  
 canicola (canine), 187  
 Chitral, 365  
 Choix, 347  
 dandy, 373  
 desert, 407  
 dum-dum, 110  
 elephantoid, 307  
 eruptive, 351  
 exanthematous, 351  
 field, 184  
 fourth venereal, 393  
 Japanese river, 356  
 junge yellow, 380  
 kedane, 356  
 march, 184  
     FE-A, 186  
     FE-B, 187  
 nine-mile, 360  
 Oroya, 400–402  
 pappataci (sandfly), 18, 365–372  
 phlebotomus, 365  
 Q, 360–364  
 Queensland coastal, 356  
 redwater, 60  
 relapsing, 159  
 remittent, 159  
 slime, 184  
 spirillum, 159  
 thermic, 444  
 tick-borne relapsing, 18, 159–173  
 Tobia, 347  
 Filarial larvae, 319  
 Filariata, 303  
 Filariasis, 303–318  
     Ozzardi, 318  
 Filatov-Koplik spots, 377  
 Fish intermediaries of  
     metagonimosis, 256  
     nanophyetosis, 263  
 Flavoquine, 91  
 Flicid, 372  
 Flies, mangrove, 314  
     tsetse, 145  
 Flukes  
     amphistome, 286  
     Fasciola 269  
     liver, 247  
     lung, 265  
 Folic acid, 429  
 Fournau 309 (antrypol), 150,  
     313  
 Fournau 270 (tryparsamide)  
 Frambesia, framboesia, 191  
 Fuadin, 235, 236, 251  
 Fumigation, 389  
 Fungi, carnivorous, 302  
 Fungi druses, 405  
 Gametes, 25  
 Gametocytes, 25, 26  
 Gangosa, 196  
 Gastrodisciasis, 284  
 Gastrodiscoides hominis, 284  
 Gentian violet, 251, 323  
 Germanin (antrypol)  
 Giardia lamblia, 203  
 Glossina palpalis (tsetse fly), 145, 146,  
     147, 152  
 Glossitis, in sprue, 423, 425  
 Gnathostoma, 340  
 Gnats, 311  
 Godovik, 134  
 Golgi scheme, plasmodia  
     development, 47  
 Gongylonema, 339  
 Gongylonematosis, 339  
 Goundou, 196  
 Granuloma,  
     genitoulcerative, 396  
     inguinale, 396–399  
     paracoccidioid, 406  
     pudenda tropicum, 296  
     symptom in yaws, 198  
     venereum, 396  
 Granulomatous                      endolymphangitis,  
     322  
 Guinea worm, 324  
     removal of, 329  
 Haemogogus equinus, 383  
     spgazzini, 383  
 Heat stroke, 444  
 Heliotrin, 438  
 Heliotropium lasiocarpum, 438  
 Hemoglobinuria, malarial, 60–64  
 Hepaticola hepatica, 332  
 Hepatitis, heliotrope, 437  
 Heptylresorcinol, 279, 300, 301, 341  
 Heterophyes heterophyes, 260  
 Heterophysiasis, 260–262  
 Hetrazan (diltrazin), 309, 313, 314, 317,  
     318, 339  
 Hexachlorane, 172  
 Hexachloroethane, 251, 254, 275  
 Hill diarrhea, 420  
 Himasthla müchlensi, 283  
 Himasthlosiasis, 283  
 Histoplasma capsulatum, 409  
     piriformis, 409  
 Histoplasmosis, 125, 409  
 Hookworms, 293–302  
 Hormones, corticosteroid, 224  
 Hydroa vaccini-forme, 456  
 Hyperergia, immunogenic,  
 in pathogenesis of malarial coma, 69  
 Hyperpyrexia, heat, 444, 446

**Immunity**, 47  
**Infections**  
     cosmopolitan, 18  
     endemic, 18  
     evolution, 20  
     with natural foci, 18  
**Insolation**, 440, 456–458  
**Insulin-glucose therapy**, 440  
**Iron, carbonate**, 299  
     reduced, 299  
**Itch**,  
     bather's, 242  
     swamp, 242  
     swimmer's, 242  
     water, 242  
**Jaundice**  
     hemolytic, 78  
     metamalarial, 78  
     spirochetel, 174, 176–183  
     splenitis, 77  
**Jinja-flies**, 311  
**Kakke**, 430  
**Kala-azar**, 79, 108, 118, 122  
     vectors in the U.S.S.R., 114  
**Kala-dukh**, 110  
**Kala-ywar**, 110  
**Karakurt**, 411–415  
**Kernig's sign**, 391  
**Kidney worm**, 343  
**Kidneys, in spirochetel jaundice**, 180  
**K soap**, 372  
**Kupffer cells, enlargement**, 387  
**Lagochilascaridosis**, 331–341  
**Lagochilascaris minor**, 331  
**Lamblia intestinalis**, 203  
     filarial 319  
**Larva migrans**, 340  
**Lasicarpine**, 438  
**Latrodectus 13-guttatus**, 412  
**Leishmania brasiliensis**, 142  
     donovani, 111  
     flagellate stages, 109  
     nilotica, 144  
     tropica, 131  
**Leishmaniasis**, 18  
     cutaneous, 130  
         American, 142  
         Brazilian, 143  
         children's, 110  
         clinical forms of, 133  
         pathogen of, 131  
         simulation of dermatoses, 136  
         Sudanese (Egyptian), 144  
         treatment of, 141–142  
         types of, 135  
         urban, 133  
         infantile, 116, 118, 122  
             clinical forms of, 122  
             complications, 123  
             course of, 119  
         visceral, 110–129  
**Leishmanioma**, 133  
**Leishmaniosis typica rusticanus**, 135  
     urbana, 133  
**Leishmanoids**, 110, 120  
**Leptomonads (see Leishmania)**  
**Leptospira**, 175  
**Leptospire**, 175–177, 182, 184, 186–190  
**Leptospirosis**, 174  
     Akiyami, 188  
     andaman, 189  
     Australian Ballico, 189  
     Batavian, 189  
     epidemic, 184  
     Hasamiyami, 188  
     icteric, 174  
     icterohaemorrhagica, 176–183  
     Japanese, 188  
     Javanese, 189  
     Palestine, 190  
     Rachmat, 189  
     Salinem, 189  
     Swart van Tienen, 189  
     water grippo-typhosal, 184–186  
     Zanoni, 189  
**Levomycetin (chloromycetin, chloramphenicol)**, 224, 363  
**Leyden-Westphal ataxia**, 96  
**Lipocain**, 238, 440  
**Liver, status in**  
     amebiasis, 213  
     fascioliasis, 271  
     malaria, 42  
     spirochetel jaundice, 180  
**Loaiasis**, 314  
**Loa loa**, 314  
**Lucanthone (nilodin)**, 237  
**Lymphogranulomatosis, inguinal**, 393–395  
**Madura foot (maduromycosis)**, 404  
**Madurella**, 404  
**Magnesium sulfate**, 414  
**Malaria**, 18, 21–107  
     acute cachexia in, 78  
     acute psychoses in, 70  
     algid, malignant, 43  
     allergies, 49  
     avian, 22  
     bilious form, 60  
     blood and blood system, 71, 72  
     cardiovascular system in, 74, 75  
     carriers of, 52, 53  
     cerebral form, 69, 70  
     classification, 53

- clinical forms, 39
- comatose, 66–69
- congenital, 54
- diagnosis
  - thick smear method, 86
- early relapses, 48
- ear trouble in, 77
- effect on pregnancy, 79, 80
- experimental, 83
- falciparum, 26, 33, 39, 40, 42–43
- gastrointestinal form of, 64, 65
- gastrointestinal tract in, 74
- hemorrhagic forms of, 65, 66
- in childhood, 81, 82
- initial (primary), 54
- inoculated, 55
- interparoxysmal period of, 50
- kidneys in, 75
- larvata, 57
- latent, form of, 57
- latent period of infection, 48
- liver in, 42, 73, 74
- malignant (falciparum)
  - algid type of, 40, 42–43
- melano-flocculation test, 97
- merulation cycle, 84
- nervous system lesions in, 76
- ophthalmic lesions in, 76
- parasites, 22
  - exoerythrocytic stages of, 24
  - in bone marrow and blood, 51
- paroxysmal period, 49
- plasmodia, 22
- postmalarial conditions, 58
- protracted, 55, 56
- psychopathologic syndromes, 70
- quartana, 39
- re-infection, 55
- relapses, 25
- secondary latent, 57
- serological tests for, 86
- spleen in, 72, 73
- symptoms of, 42
- tertiana, 39
- theories concerning, 51
- therapy, principles of, 87–91
- trophozoite cycle (see merulation)
- tropica (see falciparum)
- typhoid-like forms of, 59
- Malate or iron, 299
- Malmignatte, 412
- Mansonella ozzardi, 318
- Mansonelliasis, 318
- Mask, amaryl, 384
- Melania libertina, 256
- Mel B (arsobal), 151
- Mel W, 151
- Mepacrine (acrichin), 91
- Mercusal injection, 436
- Mercusalotherapy, 440
- Merozoites, 24, 43, 47, 49
- Metacercaris, 258, 265
- Metagonimosis, 256–259
  - fish intermediaries of, 256
- Metagonomus yokogawai, 256
- Methionine, 238, 440
- Methoxyquinoline, 22
- Miaquin (amodiaquin), 91
- Microfilaria, 303, 305, 308, 309, 311–315, 317, 325
  - demonstration of, 308
  - diurna, 314
  - nocturna, 305
  - ocular complications, 312
- Midges, 316–318
- Miracidia, 226, 227, 261, 277
- Miracidium fasciola, 270
- Miracil D, 237, 238, 241
- Mites, trombicula (velvet), 360
- Monilia psilosis, 424
  - candida yeasts, 425
- Moranyl (antrypol)
- Morphine, 415
- Morula, 25
- Mosquitoes, Anopheles, 24
  - mansonia, 305
  - swarming period, 35
- Myagawanella
  - lymphogranulomatis, 393
  - psittaci, 390
- Mycetoma (maduromycosis), 404
- Mycoses, 404–410
- Nanophyetes schichobalowi, 263
- Nanophyetosis, 263
  - fish intermediaries of, 263
- Nanukayami, 188
- Natural foci of worm diseases, 19
- Necatoriasis, 293–302
- Neoantimosan (fuadin)
- Neoarsphenamine (novarsenol), 171
- Neosalvarsan (neoarsenol), 201, 290
- Neostibosan, 127
- Nilodin, 237
- Nissl granules, 427
- Nivachin B, 105
- Notecin (hetrazan)
- Novarsenol, 171
- Novatoxyl (tryparsamide), 150
- Novocain, 414
- Nucleolus, 25
- Nystatin, 407, 409, 410
- Oesophagostomum, 336
- Onchocerca, 310, 313
- Onchocercoma, 314
- Oncosphere, 291
- Oökinete, 27

Opisthorchiasis,  
     noverca, 255  
     viverrini, 253, 254  
 Oriental sore (button), 108, 130  
 Orizanine, 431  
 Orsanine (tryparsamide), 150  
 Osarsol, 171, 218  
  
 Paludrine, 91  
 Pancreatin, 429  
 Panstrongylus megistus, 153  
 Paracoccidioides brasiliensis, 406  
 Paracoccidioidomycoses, 406  
 Paragonimiasis, 264–268  
     pulmonary, 266  
 Paragonimus westermani, 264  
 Paranephritic block, 415  
 Parathyriocrin, 429  
 Paris green, 242  
 Pellagra, 220, 221, 435  
 Pendinka (cutaneous leishmaniasis)  
 Penicillin, 183, 186, 199, 202, 224, 310, 402  
 Pentamidine-isethionate, 150, 151  
 Pentostam, 126  
 Peruvian wart, 400  
 Phenothiazine, 329  
 Phlebotomus sandflies, 110–113, 131, 365–372, 401  
 Physaloptera caucasica, 341  
 Pian (yaws)  
 Pick's sign, 368  
 Pinta, 200–201  
     fever, 347  
 Piradus cingulatus, 256  
 Pituitrin, 429  
 Plagiorchiasis, 285  
 Plasmochin, 23  
 Plasmocide, 23, 91  
     contraindications, 97  
     side effects, 96, 97  
     therapeutic properties of, 96  
 Plasmodia  
     asexual forms, 25  
     cysts, 27  
     erythrocytic cycle, 24  
     gametocytic cycle, 26  
     laboratory diagnosis, 32, 33  
     macrogametocytes (female), 27  
     male gametocytes, 27  
     ring form, 25, 43  
     sexual forms, 25  
     sporogony cycle, 32  
     tissue (exoerythrocytic) cycle, 24  
 Plasmodium  
     brasilianum, 23  
     cynomolgi, 23  
     falciparum, 22–25  
     inui, 23  
     knowlesi, 23  
     malariae, 23–25, 40  
     ovale, 23–25, 39  
     reichenowi, 23  
     rodhaini, 23  
     schwetzi, 24  
     vivax, 23–25, 39, 43  
 Pleurocercoid larva, 288, 289  
 Poisonous fauna, 411–419  
 Poisons, contact, 371  
 Polycirrhosis, 58  
 Polyendocrinopathy, 425  
 Poradenitis, 393  
 Potassium iodide, 407  
 Premunition, 47, 49, 85, 140  
 Primaquine, 23, 91  
     contraindications, 98  
     prophylactic course, 107  
     side effects, 98  
     therapeutic properties, 98  
 Procaine penicillin G, 199  
 Promedol, 415  
 Pseudoelephantiasis, 398  
 Psilosis, 420  
 Psittacosis, 390–392  
     rickettsiaformis, 390  
 Psychoses,  
     acrichin, 93  
     malarial, acute, 70  
 Puncture, sternal, 124  
 Pyrethrin, 371  
     candles, 372  
 Pyrethrum flowers, 371  
 Pyrimethamine (chloridin), 91, 144  
  
 Quinacrine (acrichin), 91, 141  
 Quinamine, 217  
 Quinine, 91  
     dosage of, 102, 104  
     idiosyncratic reaction to, 100  
     side effects of, 99  
     therapeutic properties of, 99  
 Quinocide, 23, 91  
     dosage of, 103  
     side effects of, 103  
     prophylactic course, 107  
     therapeutic properties of, 98  
 Quinoline, 22  
  
 Raillietina tapeworms, 292  
 Raillietiniasis, 292  
 Raspberry jelly stoll, 213  
 Rectoromanoscopy in  
     chronic ulcerative colitis, 223  
 Redia, 261  
 Repellants, insect, 372  
 Resochin, 105  
 Resoquine, 105  
 Rhabditoid larvae, 319

- Rhinopharyngitis mutilans (gangosa)  
 Rhipicephalus sanguineus, 351, 355  
 Rickettsia, 344–364  
     burneti, 360  
     conori, 351  
     mooseri, 345  
     orientalis, 356  
 Rickettsioses, 344–364  
 Ripodral, 235  
 Rishta, 324  
 Rivanol, 216, 224  
 Romanovsky stain, 24  
 Rusell's bodies, 405
- Salmonella, 402  
     secondary infection, 401  
 Salvarsan, 171  
 Sandflies (Phlebotomus), 109, 131, 401  
 Sandfly bites, idiosyncrasy to, 138  
 Schistosoma haematobium, mansoni,  
     japonicum, 226–245  
 Schistosomal hematuria, 227  
 Schistosome dermatitis, 242–245  
 Schistosomiasis, 226–245  
     genitourinary, 226–231, 235–238  
     intestinal, 231–238  
     Japanese, 238  
 Schistosomule, 226, 227  
 Schizont, 24–26  
 Schulman method, demonstration of  
     strongyloid larvae, 321  
 Scorpions, 415–416  
 Scurvy, 435  
 Ship beriberi, 431, 434  
 Shoshin, 431, 433  
 Sleeping sickness, 148  
 Snails,  
     Australorbis, 233  
     Biomphalaria, 233  
     Bulinus, 228, 233  
     Bythinia, 247  
     intermediaries of  
         echinostomata, 280  
         fasciolopsis, 276  
         heterophyasis, 261  
         metagonimosis, 263  
         paragonimiasis, 265  
     Limnaea, 243  
     Oncomelania, 238  
     Physopsis, 228, 233  
     Planorbis, 228, 233, 276  
     Tropicorbis, 233  
 Snakes, venomous, 417–419  
 Snakebite, treatment, 419  
 Sodium stibogluconate, 126  
 Solustibosan, 126  
 Solusurmin, 126  
 Sparganosis, 288–290  
 Sparganum proliferum, 288
- Spider, Black Widow, 411  
 Spirochaeta, spirochetes, 159–163,  
     165–168, 171, 174  
 Spirochetosis, 159  
 Spleen in  
     fascioliasis, 271  
     malaria, 42  
     spirochetal jaundice, 180  
     tick-borne relapsing fevers, 170  
 Splenic adenofibrosis, 77  
 Splenomegaly  
     complications, 73  
     in leishmaniasis, 124  
     metamalarial, 78  
 Sporocysts, 261  
 Sporogony, 25, 26, 32  
 Sporozoites, 24  
 Sprue, 220, 221, 420–425, 435  
     treatment of, 428  
 Stagnicola emarginata angulata, 243  
 Stegomyia (Aedes)  
 Stibophen (fuadin)  
 Streptomycin, 224, 310, 398, 402  
 Strongylidae, 336  
 Strongyloid larvae, demonstration, 321  
 Strongyloides stercoris, 319  
 Strongyloidiasis, 319–323  
 Strongyloidosis, 336  
 Strophanthin, 415, 447  
 Strychnine, 436  
 Sulfadiazine (sulfazin), 395, 407  
 Sulfa drugs, 224  
 Sulfamerazine, 407  
 Sulfapyridine (sulfidin), 395  
 Sulfathiazine (sulfadimezin), 395  
 Sulfathiazole (norsulfazol), 395  
 Sunstroke, 444, 445  
 Syndrome, hepatolienal, 58, 72  
 Syngamus laryngeus, 338  
 Synthomycin, 395  
 Syphilis, endemic, 202
- Tace noire, 351–353  
 Tartar emetic, 235, 241  
 Ternidens deminutus, 336  
 Terramycin, 199, 219, 224, 350, 354, 359,  
     392, 395  
 Test  
     agglutination, 363  
     allergic, 410  
     Frei, 394  
     Henry's, 87  
     neutralisation, 381  
     Olsmeier, 433  
     subcutaneous allergic, 363  
 Tetrachloroethylene, 259, 279, 280, 282,  
     284, 300, 335, 337  
 Tetrachloromethane, 300  
 Thelaziasis, 342

Thymol, 249, 259, 262, 263, 279, 280, 282, 284, 300, 301, 335

Ticks,  
  Argasidae, 348  
  Aribatidae, 291  
  canine, 351, 355  
  Ixodidae, 348  
  Ornithodoros, 18, 160–167, 172, 173

Tinctura ferri pomati, 299

Tissue plasmodia, 24

Torula yeasts, 425

Toxicosis alimentary, 437–441

Transovarial transmission, 163

Treponema carateum, 200

Triatome megista, 153

Trichinella larvae, 273

Trichinosis, 273

Trichobilharzia, 243

Trichocephalus hepaticus, 332

Trichostrongylidae, 334

Trophozoites, 43

Trypanosoma, 145  
  cruzi, 153  
  gambiense, 145–149  
  rhodesiensis, 145–149

Trypanosomes,  
  vectors of, 154  
  species in human blood, 153

Trypanosomiasis, 145–158

Tryparsamide, 150

Tryparson (tryparsamide)

Tryponarsyl (tryparsamide)

Trypotan (tryparsamide)

Typhus, 347, 356  
  mite, 356  
  scrub, 344

Urinalysis, in malarial  
  hemoglobinuria, 63

Urinary bilharziasis, 227

Uta, 142

Venomous snakes, 417–419

Verruga peruana, 400, 401

Viscerophilus dengue, 374  
  tropicus, 380

Vitamin B<sub>12</sub>, 238

Watsoniasis, 286

Watsonius watsoni, 286

Weil-Felix reaction, 346

Wuchereriasis, 303–310

Xenorganism, 19

Xeroderma, 311

Yatren, 216, 218, 224

Yaws, 191–199  
  clinical symptoms, international  
  differentiation from syphilis, 198  
  mother, 194  
  nomenclature, 193–194  
  treatment of, 199

Zygote, 27

---